Volume 14, Number 5
NOVEMBER 1953

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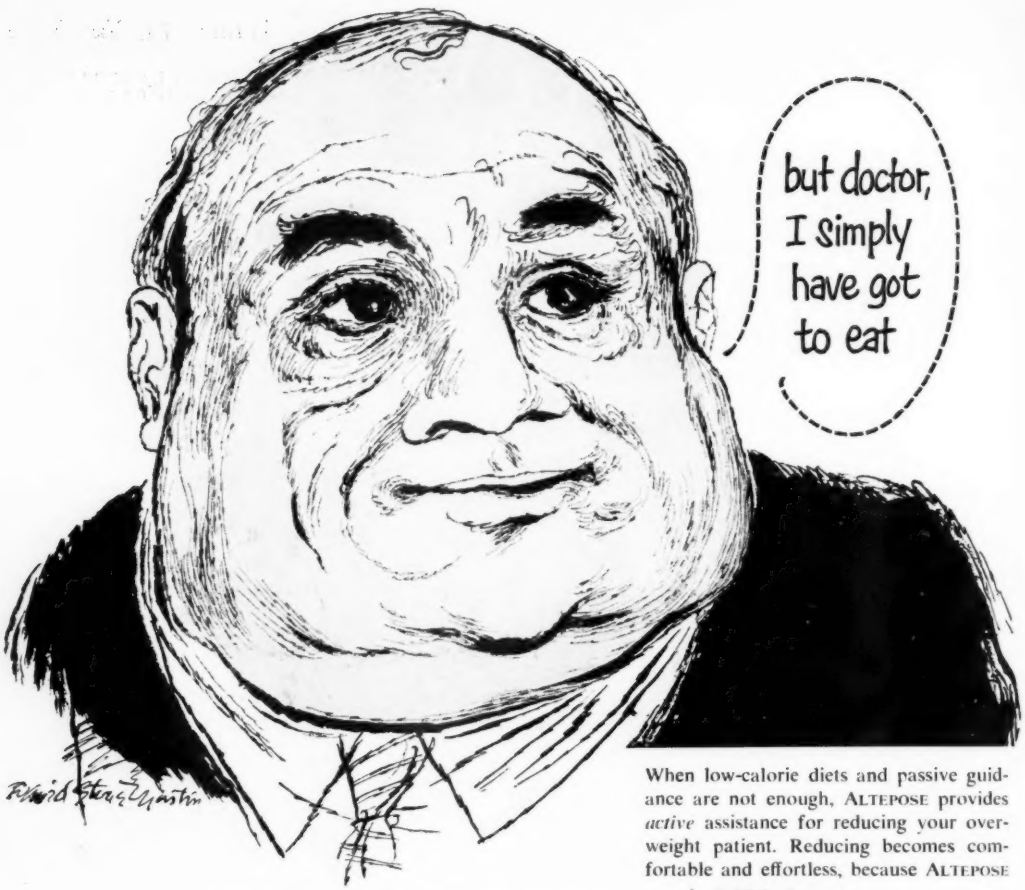

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References: 1. Jolliffe, N.: Reduce and *Stay* Reduced. Simon and Schuster. New York, 1952. p. 2. **2.** Tainter, M. L.: J. Nutrition 27:89, Jan. 1944. **3.** Kalb, S. W.: M. Soc. New Jersey 39:584, Nov. 1942.

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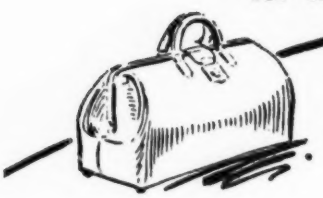

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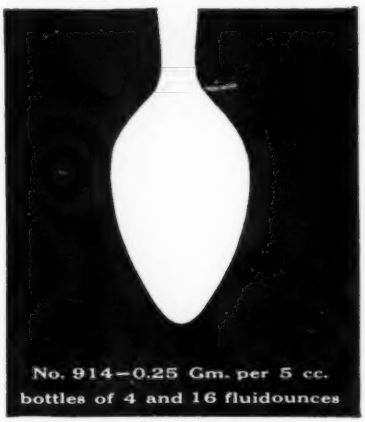

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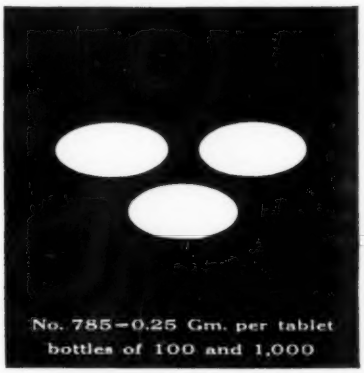

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Your Questions answered

Readers may send questions from their own practice or other medical problems which will be answered by qualified consultants.

• PARKINSONISM

Question: For about 2 years the patient, a 59 year old man, has been suffering from a neuromuscular disorder, especially of the left hand. There is some tremor. There seems to be no loss of sensation in the hand and the patient can catch things and easily hold weights in his hands up to 30 pounds. His general health is good but he complains of a feeling of weakness.

The following medication has been given:

Vitamin B_1 (100 mg. per cubic centimeter) 1 cc. daily for 30 days, intramuscularly

HYPOBITA® (Sharp & Dohme vitamin C complex) 30 cc.

Potassium iodide mixture, 4 oz.

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M.D.—Calcutta, India

ANSWER: I suspect that the patient described is suffering from parkinsonism, since in spite of his tremor and weakness he is able to catch things and to hold heavy objects. There is no specific treatment for the condition although intracranial obliteration of the anterior choroidal artery has recently been reported by Doctor Irving S. Cooper as effective in relieving severe parkinsonian conditions. The most reliable medicine is ARTANE®, 2 mg. to 5 mg. 3 to 5 times a day. depending on tolerance, reinforced by a combination of BENADRYL®, 25 to 50 mg. twice a day, and DEXEDRINE®, 5 mg. in the morning and at noon. Barbiturates should be avoided and vitamins are of very limited value.

WALTER FREEMAN

• SENILE RETINAL DEGENERATION

Question: The patient, a 63 year old woman of nervous temperament, has been examined by an ophthalmologist who found that her right eye showed senile retinal degeneration around the whole macular area. Some similar changes are starting to take place in the left eye. In view of the failing eyesight, this patient is quite concerned about eventual blindness. She is in good health otherwise. Will cortisone or ACTH be beneficial in this case?

M.D.—Saskatchewan

ANSWER: Senile macular retinal degeneration is considered to be due to sclerosis of the choroidal vessels that supply the area. It is, therefore, a degenerative disease seldom associated with complete blindness, since the peripheral vision remains good throughout the rest of the patient's life in the vast majority of cases. Cortisone or ACTH, or any other treatment, so far as is known, has no influence on the course of the disease. This is particularly true of ACTH and cortisone, since the disease is not an inflammatory one.

DERRICK VAIL

• PAPILLOMA OF LARYNX

Question: Is surgery or x-ray therapy the treatment of choice in a case of papilloma of the larynx? The patient is a 44 year old white woman with a history of surgery for papilloma of the larynx in 1951 (anterior one-third); operation was repeated 9 months later, and now, after 8 months, a papilloma is present again.

M.D.—Missouri

ANSWER: Papilloma of the larynx (vocal cords) is prone to recur. Radiation does not control this lesion. If recurrences can be removed through the laryngoscope, they should be excised through this instrument. Microscopic examination should be done on each occasion since squamous carcinoma may appear at any time. If necessary a laryngofissure may be performed and a cordectomy, unilateral or bilateral as indicated, may be carried out. The voice of a patient undergoing such a procedure never returns to normal. but this is of secondary importance. The patient should be kept under close observation.

W. S. MACCOMB

(Continued on page A-36)

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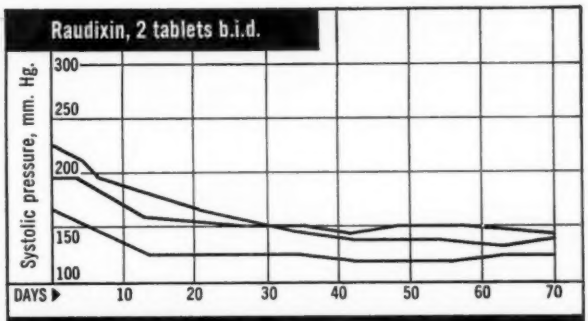
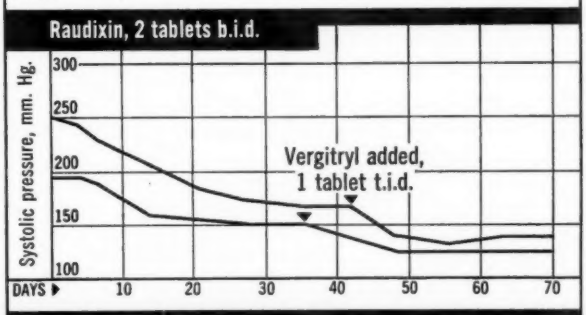


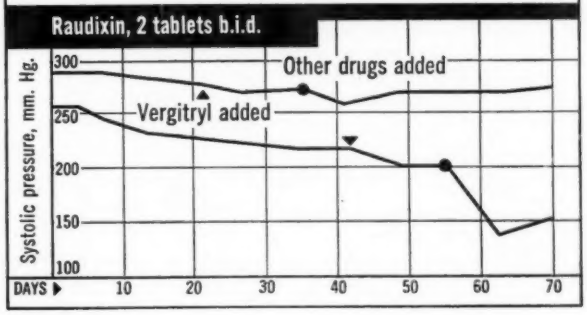
step 2

If blood pressure is not adequately controlled in four to eight weeks, Vergitryl (veratrum) may be added to Raudixin. This brings many of the remaining patients under control. Raudixin tends to delay tolerance to Veratrum, and makes smaller dosage possible.



step 3

For the few patients resistant to this combined regimen, a more potent drug may be added, for example, Bistrium (hexamethonium). The most potent drugs, which are potentially dangerous, are thus used only as a last resort in the most refractory cases.



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• UTERINE HEMORRHAGE

Question: One month ago a 35 year old female was helped into my office in a state of shock and collapse with a tentative diagnosis of "uterine hemorrhage due to fibroids."

The patient gave a history of profuse vaginal bleeding 1 month prior followed by 4 to 5 days of very scanty show, then profuse hemorrhage for 20 days, when she was told to consult me.

Examination showed an exsanguinated female; blood pressure 100/40; pulse 100; temperature 100.6° F.; uterus not enlarged but soft and boggy; vaginal vault filled with black, foul smelling clots and fresh blood from the cervix.

The patient was hospitalized immediately with a tentative diagnosis of incomplete abortion; blood count on admission was 2,000,000 red cells. She was typed, transfused, curetted, and given 3 more pints of blood. Microscopic examination of the material gave no recognizable evidence of recent gestation. The patient made an uneventful recovery.

Twenty-seven days later the patient started to hemorrhage profusely from cervix and also presented many areas of ecchymosis the size of a dime to a dollar on arms, thighs, and buttocks. Microscopic examination of the blood revealed the following:

Red blood cells: 4,440,000
Hemoglobin: 72% . . . 11.6 gm.
Platelets: 53,280
Color index: .81
White cells: 6600
Neutrophils: 62%
16% stab; 46% segmented; 31% lymphocyte; 6% monocyte; 1% eosinophil
Schilling index: 1/2.8
Multiple index: 5/7
Neutrophils showed slightly ragged nuclei.

Progesterone and androgens controlled the bleeding and the areas of ecchymosis cleared up. The spleen is enlarged.

In the light of more modern medicines, what is the best way to treat this patient?

M.D.—California

ANSWER: It seems to me that the first hemorrhage that occurred in the case of the 35 year old female who was helped into the physician's office in a state of shock and collapse may have been due to miscarriage. It is probable that the treatment at the time, which consisted partly of a dilatation and curettage and partly of transfusion, was correct and that the hemorrhage was taken care of by the treatment which was followed. The hemorrhage which occurred about a month later may have been due to a different procedure. It seems to me that the bleeding may have been due to some disturbance in the blood forming organs. I am inclined to think that the patient has some splenic trouble which is probably associated with thrombocytopenic purpura which was possibly helped by progesterone and androgens and which was associated with areas of ecchymosis.

I would suggest that the bleeding time and clot retraction be determined and that if the patient's condition permits, a splenectomy would be in order. I would advise the use of rutin, vitamin C and vitamin K and a sternal tap so that the bone marrow can be studied to see if there is any essential change. It is possible that the use of cortisone may be of value. Whether or not an operation which would prevent any more cyclic bleeding, such as hysterectomy, needs to be done would depend on the examination following splenectomy.

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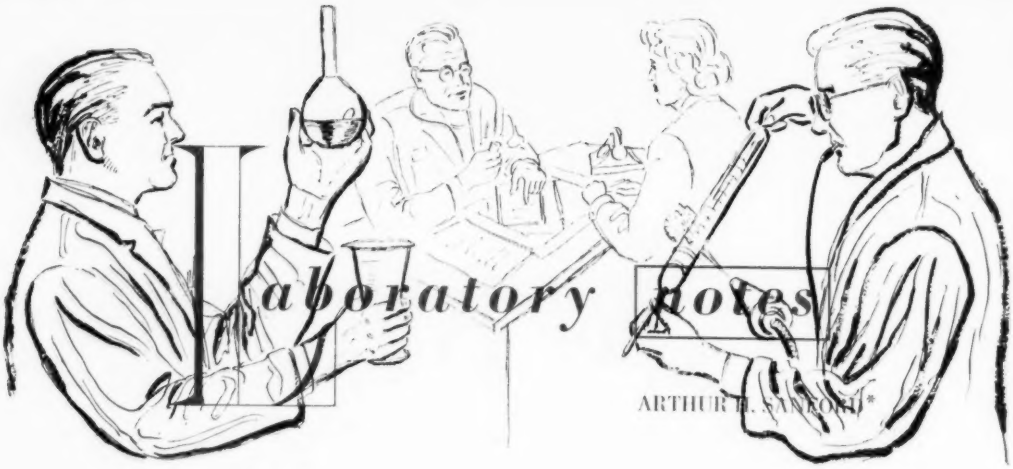

ARTHUR H. SANFORD*

HEMATOLOGY

There are a number of important facts connected with hematology which I shall discuss with you from time to time. The circulating blood is surely the life-giving stream, and hemoglobin has been said to be the most important single chemical substance in the body. It is measured in grams per hundred milliliters, while many other substances are measured only in milligrams. Some accurate method of measuring this substance is important.

Instruments

Instruments which depend on the visual matching of colors all give results only approximately correct. Such methods are sufficient to determine whether a person is anemic. However, in anemia or polycythemia, it is important to have an accurate record of the hemoglobin content in grams per cent. Some photoelectric colorimeter will do this most accurately. There is a variation in the reliability of cheaper instruments, and each instrument must be calibrated against a standard accurate method, such as Van Slyke's oxygen capacity or Wong's iron method. A reliably constructed instrument must be kept in good working order and checked from time to time with some other method.

Staining Technics

It has been said that an accurate estimation of the concentration of hemoglobin with an intelligent study of the stained film will yield 90 per cent of all the diagnostic information obtainable by examination of the blood. However, it is important that the physician or his technologist make good "smears." This inelegant word is often too expressive of the thick, poorly prepared slides that are forwarded to hematologists for study. Medical students are not usually adequately trained in, nor do hospital residents or interns have time to acquire, a good technic in the preparation of satisfactory blood films. Attention to a few simple rules may result in the acquisition of an interesting skill of which the physician may be proud, and which may then be taught to the laboratory assistant, if she has not already been able to teach him.

The first requisite is to have clean slides. New slides should be soaked in a 10 per cent solution of acetic acid to remove free alkali and then rinsed in clean distilled water and dried thoroughly. Old slides may be washed in soap and water, rubbed with alcohol and dried with a clean towel. Secondly, the drop of blood should be placed near the end of a clean, dry slide. This must be spread quickly before coagulation takes place. The little trick of spreading the film must be acquired by practice. No amount of description can teach anyone how to do it. A second slide is used as the "spreader." Hold this slide at an angle of 30 to 40 degrees and draw it up against the drop of blood, which will immediately run across the end. Push the "spreader" along the slide rather rapidly. The blood will follow. The thickness of the film can be regulated by changing the angle, by varying the pressure and by using a smaller or larger drop of blood; however, an attempt should be made to keep the film thin.

Unstained slides may be referred to some laboratory for study. But why not have the pleasure of taking the third step, in your own office laboratory, and staining the film with that beauti-

(Continued on page A-55)

*Emeritus Staff, Division of Clinical Pathology, Mayo Clinic; Director of Laboratories, Rochester State Hospital, Rochester, Minnesota.

ful Romanowsky stain or Wright's stain. James Homer Wright (Boston, 1869-1928) was the pathologist at Massachusetts General Hospital. He was associated with Frank B. Mallory and was co-author of a well known textbook, published first in 1897 (Mallory, F. B. and Wright. J. H.: "Pathological Technique. A Practical Manual for the Pathological Laboratory"). He described his stain, which he called "a simplification of Leishman's stain" in 1902 (J. M. Research 7:138-144, 1902). Wright was a good clinical pathologist, but he was not a prolific writer. He will always be remembered for the excellent stain which he developed.

Properly used, this stain yields a preparation which cannot be equaled for blue, red and azure colors by any other stain. It is not always possible to purchase good Wright's stain in solution. The Paragon Company, New York, advertises a properly aged stain, each lot of which has been tested by staining blood cells. Colman and Bell, Norwood, Ohio, makes excellent Wright's stain. This may be purchased dry and dissolved in methyl alcohol, as described in all textbooks, or it may be purchased in solution. The methyl alcohol solvent is also the fixative of the blood film. The slide should be placed over 2 glass rods over a sink or other support where the whole process can be carried out without moving the slide. Put the undiluted stain on the slide for 1, 2 or 3 minutes. One minute will not stain very heavily. while a longer time will result in very distinct blue staining of all nuclei, After this preliminary fixation and staining, add the same amount of diluent. This may be distilled water (never tap water) but preferably McJunkin's buffer solution. This solution, with a *p*H of 6.4, brings out beautifully the eosin of the azure granules. Many technologists blow gently on the slide at this step. This mixes the stain and a metallic scum appears. The time of staining with the diluted stain should be 4 or 5 minutes. Trial and accurate attention to time will determine which combination yields the best results in your hands and with your particular batch of stain. The buffer solution is prepared by dissolving 6.63 gm. of monobasic potassium phosphate and 3.20 gm. of dibasic sodium phosphate in 1 liter of water.

This may all sound complicated, but it is not. Help your technologist or let her help you to master the trick of making good Wright-stained blood slides, and the oil immersion lens on your expensive microscope will show you a picture of which you will be proud.

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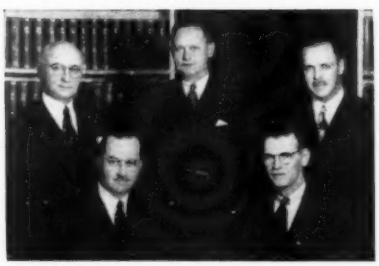

Dr. Francis E. LeJeune—Dr. Curtis Tyrone—Dr. Alton Ochsner (back row); Dr. Edgar Burns—Dr. Guy A. Caldwell (seated).

THE importance of postgraduate instruction is being appreciated more and more. Medicine as much as or even more than any other science is making tremendous advances and unless a practitioner of the healing art makes every attempt to keep abreast of the times and keep informed of the new advances, his efforts will become increasingly less effectual.

With the introduction of antibiotics, infections are much less important than previously, but increasing attention is being focused on degenerative diseases because of the increase in life expectancy. At the present time, geriatrics is a prominent part of the practice of medicine. Moreover, with a better understanding of disease, much greater emphasis is being placed on prophylaxis than previously, and it is hoped that in the future many more illnesses than now can be prevented.

We are indeed fortunate to be citizens of a nation which encourages complete freedom of thought and whose people contribute so willingly and so generously to the welfare of the nation. This is particularly reflected in the voluntary agencies which are interested in health problems and which are financed entirely by voluntary donations from the public. It is through the educational programs of these organizations and the funds donated by them that much of the research conducted today can be done.

POSTGRADUATE MEDICINE is doing an excellent job in disseminating information to the medical profession, and we in the deep South are indeed happy to be asked to participate in the work which they are doing.

ALTON OCHSNER, M.D.
Guest Editor

Management of the Postmenopausal Woman

JOHN C. WEED*

Ochsner Clinic, New Orleans, Louisiana

The management of the postmenopausal woman consists of understanding not only her physical ailments but her emotional background as well. Treatment must be directed toward alleviation of physical suffering, reassurance and supportive therapy, rather than haphazard hormone administration. Periodic examination aids in reassuring this group of patients.

JOHN C. WEED

THE woman in the postmenopausal era of her life has many problems which may affect her emotional stability. Expectation of a trying period is often engendered by tales of female relatives or friends who have had distressing symptoms in "the change." Coupled with the harrowing nervousness, insomnia and hot flashes is the widespread fear of cancer that many women now have. Most of these fears are the result of lack of authentic information concerning the menopause or of half-knowledge, some of which is propagated through current lay periodicals. Partly, however, physicians are at fault because they will not devote a few moments to explaining the physiologic changes, and correcting misinformation about cancer in the female.

On entering the menopausal state, the patient may have reached a zenith in her productive life, where her driving interests begin to wane. Her family is complete, often grown, depriving her of an interest which previously occupied much of her time. Competition with other women seems less important at this age, and those active in civic or religious endeavors have probably by this time achieved their goal in such activities. Hence, these women often have few extracurricular interests or household duties to occupy their minds. Such a change, however gradual it may be, produces a feeling of insecurity, anxiety or restlessness. Later the characteristic hot flashes appear and the syndrome becomes complete. It is interesting to note the wide range in ages of patients with hot flashes, 35 to 70 years, and their complete irrelevance to the menopause itself.

Not only may anxiety be related to the emotional state of the patient but it may also concern her physical health. With the menopause comes awareness of her inability to perform physical tasks as easily as previously, and perhaps cardiovascular or arthritic changes have developed. However, the chief source of anxiety lies in her fear of cancer.

Problems besetting the postmenopausal patient which may have a physical basis may be divided for discussion into local irritation,

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vaginal bleeding, pelvic discomfort and coital disturbances. Of these the first is the most common.

Local irritation may involve only the labia, but often extends to the perianal region and groins. The obese patient particularly is prone to vulvar and inguinal pruritus, often accepting the symptom as part of her due. Fungous infections of the groin, vulva or vagina occur more often in obese than in thin women. Diabetes mellitus, or abnormal sugar tolerance, should be excluded. Leukoplakia, vulvitis and kraurosis also occur in this age group, but are infrequent. *Trichomonas* vaginitis is less often encountered after the menopause but is a possibility. Similarly, neurodermatitis is rarely encountered but should be considered. Senile vaginitis is a more common cause of irritation in these women than other infectious processes.

Vaginal spotting or frank bleeding which recurs after an interval, assumed to be the menopause, causes great concern more often to the patient than to the physician. These women are usually so cancer-conscious that they may be greatly alarmed. Too often the physician remains complacent. Of considerable interest are those few women who menstruate regularly for a year or two after amenorrhea for several months, but whose recurring cycles differ in no way from their previous menses. Establishment of such a pattern is reassurance to both patient and physician. Unfortunately, recurrence of bleeding more often is indicative of disease, the cause of which should be carefully sought. Bleeding is still by far the earliest symptom of carcinoma of the genital tract. Great care should be exercised to exclude malignancy of the vagina, cervix, uterus and ovaries. "Functional" bleeding is a diagnosis resulting from exclusion of all other possible causes. The possibility of more than one site of origin of vaginal bleeding in this age group should be borne in mind.

Pelvic pain and pressure are sometimes the chief complaints of these women. The patient often has difficulty describing such discomfort. She may say that "her insides are falling out," "she incompletely empties her bladder," or "something presses upon the bladder or rectum." Occasionally the discomfort is referred anteriorly, occasionally to the back alone. Such complaints, although vague, should alert the physician to the possibility of pelvic relaxation, either cystocele, rectocele, uterine prolapse or a combination thereof. Extreme degrees of any of these may, however, be relatively asymptomatic. For example, procidentia is often painless, causing only the annoyance of the protruding mass.

Problems associated with sexual congress occur more often than is generally realized. It would seem that a couple, aging together, would have corresponding amounts of libido. Unfortunately, in the female, libido ceases somewhat earlier than in her mate, to her discomfiture and often to the detriment of both. Atrophic changes in the genitalia, with decrease in the lubricating function of the vulvovaginal glands, are a common cause of dyspareunia in these women. Shrinkage of the vagina, although not an important feature, in some instances may be the cause. Probably greatest, however, is the rejection a woman without libido feels subconsciously for the act. This may be reflected in vague terms of pelvic pain, nervousness or other difficulties of an emotional nature.

Of utmost importance in management of the postmenopausal woman is obtaining an adequate history. This should include such stereotyped information as the menstrual rhythm, fertility, previous operations and illnesses. From this information the physiologic pattern of the patient may be surmised, so that her present status may be adapted to that portrayed. It is of interest to know the reason for previous operations as well as their effects on the patient. Women with functional problems in early life can be expected to have similar difficulties later.

Of equal value is inquiry into the habits, activities, hobbies and domestic relations of the patient. This information may be obtained later in the interview but it is of immense importance. The patient should be encouraged to confide in her physician insofar as she can. Whether her professional or domestic environment is pleasant or difficult, whether

her husband is sympathetic, her relation to her children or neighbors—all may profoundly affect a patient in this age group. The changing responsibilities of this age group may influence these women. Grown children, a smaller house to care for, and changing interests in civic endeavors all leave a void in the patient's daily activities, both physical and mental, which may be reflected on her health. Too few women have hobbies which can be cultivated when they need them most.

Physical examination should be thorough. The gynecologist emphasizes some aspects of the physical examination which unfortunately may be overlooked or minimized by her physician. Thorough examination of the breasts and pelvis should be done in every woman in this age group. Both of these may be bypassed unless the patient particularly mentions a complaint referable to these organs or requests such an examination. The fact that cancer of the breast and of the uterus together are the leading causes of death from malignancy in the female makes it imperative to do these examinations routinely. False modesty, not only on the part of the patient but also on the part of the physician, contributes to late rather than early diagnosis. Careful inspection and palpation of the breasts require only a few minutes and offer considerable reassurance to the patient. Pelvic examination requires more effort and occasionally is met with resistance by the patient. However, the woman is rare who will not submit to this examination after a few words explaining its significance. Inspection of the external genitalia may disclose leukoplakia which the patient has tolerated for years without complaint. Biopsy of such lesions is mandatory. Speculum examination with adequate visualization of the cervix will disclose cervical polyps or ulcerations which are asymptomatic. Liberal use of the biopsy punch cannot be overemphasized. The pain produced is minimal, and most women will accept it readily with a few explanatory words. If cytologists of experience are available, vaginal smears may be made. However, the smear should not be allowed to replace the biopsy when visible or palpable lesions exist.

A careful bimanual examination is important. Determination of degree of involution of the internal genitalia, and of abnormality in size of the uterus and adnexa, as well as of the contents, if any, of the cul-de-sac, completes the examination. A rectovaginal examination is of more value for the latter than vaginal alone, and the ovaries can be more easily outlined in this manner. Any enlargement of the ovaries beyond the menopause becomes significant when one considers the average age in ovarian malignancy (57 years) and the lack of symptoms the patients exhibit.

Fresh hanging drop preparations should be made in every instance of vaginal or vulvovaginal irritation. Diagnosis of *Trichomonas* or yeast vaginitis may be readily made in this manner, with the patient at hand and ready for immediate treatment. Occasionally *Endamoeba histolytica* can be identified in such preparations.

There are 3 important features in the management of the menopausal patient. Foremost, of course, is detection and correction of pathologic states insofar as is possible. This involves a broad spectrum of degenerative processes. Adequate treatment of heart disease, arthritis, diabetes and the like is essential to the patient's continued well-being. The reduction of the obese should not be overlooked. Secondly, reassurance regarding the condition of female organs and the menopause should be given freely and frankly. Every woman, consciously or subconsciously, is aware of cancer, fears it, and knows another who has cancer. It is a real relief to be reassured that she does not have this dreaded disease.

Reassurance must be coupled with a frank discussion of the symptoms of the menopause and the factors causing these symptoms. The changing habits, desires and responses to stimuli, when exposed, help a patient understand her hot flashes, emotional irritability and insomnia. Too often the glib diagnosis of "menopausal syndrome" obscures the real problem of domestic difficulty, anxiety, depression or other neurosis. No treatment, whether by hormones, sedatives or neglect, will long benefit these women until their prob-

lem is exposed to them. Reassurance should be supported by mild sedation in many instances. It is impossible to expect the improvement following an interview to last without some help. The patient should be made to realize, however, that the sedation is a crutch, and not a permanent support.

Most patients with the menopausal syndrome need no hormones. In only a few selected cases should hormones be administered and then only by mouth. Hypodermic administration of estrogens in homeopathic doses has a profound psychic effect. If the estrogenic effect is desirable, oral administration is better controlled and more efficient. In my opinion, hypodermic administration of estrogens is seldom, if ever, necessary. Hormonal therapy may have disadvantages that outweigh its possible advantages, such as increased sensitivity of dormant breasts and recurrence of vaginal bleeding. Such symptoms only serve to increase the malaise and mental discomfort of the patient and bring her fresh problems with which to cope. Discontinuance of sporadic and ineffectual hormonal treatment has never had an unsatisfactory effect.

Rehabilitation is somewhat more difficult to achieve. This includes introduction of new interests compatible with the physical and economic status of the patient. Moreover, it involves acceptance by the patient of various truths she has refused to face, namely, that she is aging, that her decisions may be questioned by her adult children, that her sphere of control is contracting. She must be taught how to "grow old gracefully." She must be led to believe that she is still useful and that there are many civic and religious organizations in which she can be active. In this troublesome period of a woman's life, an outlet for physical energy should be found—gardening, sewing, painting or some similar hobby. A daily walk may be all the physical exercise possible. Some muscular fatigue should balance the expenditure of nervous energy.

Relief of physical complaints is more readily attained. Vaginitis due to yeast will respond to propionic acid jellies or gentian violet preparations in the absence of diabetes. *Trichomonas vaginalis* vaginitis may be controlled by a number of medications, our current preference being PHISODERM® douches (½ oz. to 1 qt. warm water) and FLORAQUIN® suppositories. Senile vaginitis may be successfully treated by virtually any estrogenic or suppository used with a cleansing douche.

Bleeding from the genital tract must be vigorously treated once the cause has been determined. Estrogenic suppositories or cremes, utilized under supervision, will restore the atrophic and ulcerated vagina to a healthy functioning organ. Local administration rarely, if ever, has any systemic effect, and minimal dosage is satisfactory.

Bleeding from the endocervical canal or the fundus uteri requires more radical treatment. Treatment of malignancies of the genital tract in this group of women differs in no way from that in their younger sisters. These older women tolerate surgical procedures well. If the cause of bleeding is obscure but is known to arise in the upper genital tract, hysterectomy and oophorectomy are preferable to procrastination. Hormonal therapy has no place in the management of these problems.

In summary, management of the postmenopausal woman consists of understanding not only her physical ailments but her emotional background as well. Only in so doing can she be led to proper adjustments. The diagnosis of menopausal syndrome heretofore has been a wastebasket for complaints, many of which are justified. Treatment with hormones without further investigation is usually unsuccessful. A sympathetic ear with a few words of advice is much more helpful. Periodic examination, at least annually, followed by reassurance, encouragement and supportive therapy offers patients of this age courage to face their own problems.

Prevention and Management of Acute Cholecystitis

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Acute cholecystitis is a common, serious disease of the biliary tract. Since recognizable chronic symptoms usually precede these attacks, dangerous acute cholecystitis can be largely prevented by performance of cholecystectomy as soon as the stones are discovered, particularly if symptomatic.

PAUL T. DECAMP

ACUTE cholecystitis may be defined as acute inflammation of the gallbladder which is commonly initiated chemically and is associated with obstruction due to cholelithiasis, but later becomes a bacterial inflammatory process. In addition to constant severe pain in the right upper abdominal quadrant extending to the back and scapula, the patient has nausea, vomiting, fever and leukocytosis. The condition may be distinguished from acute biliary colic by the developing signs of infection, the greater severity of symptoms and the unremitting progressive nature of the attack.

Acute cholecystitis constitutes from 5 to 10 per cent of the cases of surgical biliary disease, and from 20 to 25 per cent of the operations for cholecystitis are performed for the acute form of the disease. The seriousness of acute cholecystitis is evidenced by its high case fatality rate. In a recent study of 468 consecutive cases of acute cholecystitis encountered at the Charity Hospital of Louisiana in New Orleans between 1940 and 1951, the case fatality rate was 8.3 per cent for the entire series and 7.5 per cent for the 462 operative cases.[1] The case fatality rates in most large series of cases are reported to be in excess of 5 per cent.

The most significant factors influencing the operative fatality rate are the severity of the attack and the age of the patient. In our study the age-corrected operative fatality rate for extremely severe cases was 11.6 per cent as compared with 5.3 per cent and 4.5 per cent, respectively, for moderately severe and severe cases. The age factor was even more striking. No deaths were observed among 134 patients less than 40 years of age, 11 deaths occurred among 201 patients between 40 and 60 years, and there were 28 deaths among 113 patients 60 years of age or older. The observed case fatality rates for the latter 2 groups were 5.5 and 21.1 per cent, respectively. After correction for severity of disease the rates were 5.7 and 17.7 per cent. The probability of these differences occurring by chance is remote. Others have observed a similar correlation between age and case fatality rates in acute cholecystitis. Quigley[2] reported a case fatality rate of 21.4 per cent

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in 100 patients over 65 years of age, and Fisher[3] reported a rate of 23.7 per cent in 80 patients over 70 years of age.

It is thus apparent that acute cholecystitis is a relatively common, serious disease. The general case fatality rate is high and it increases rapidly with the age of the patient, partly because of age and related factors and partly because the disease assumes a more virulent form in the aged.

Prevention

The hazards of cholecystectomy for chronic cholecystitis are relatively slight, the case fatality rate being less than 1 per cent. This is particularly significant in view of the fact that approximately 80 per cent of patients with acute cholecystitis give a history of previous symptoms of cholecystitis. A large number of cases of acute cholecystitis could be prevented by performance of cholecystectomy when biliary colic or chronic symptoms of cholecystitis and cholelithiasis first appear. Additional cases could be prevented by operative removal of gallbladders containing asymptomatic stones. In view of the increasing severity of acute cholecystitis and the alarming increase in mortality in older individuals, it is imperative that elective cholecystectomy for chronic cholecystitis, a relatively safe procedure, be performed at an early age. More can be done to reduce the number of fatalities from acute cholecystitis by such prophylactic surgical treatment than by all manner of improvements in the management of the patient with established acute cholecystitis.

Management of Acute Attack

With the onset of an attack of acute cholecystitis, the patient should be hospitalized. The disease is progressive and it is frequently difficult to evaluate the severity of the pathologic process. Delay or misjudgment may permit development of advanced and complicated stages of the disease, in which the morbidity and mortality rates are naturally high. Gangrene may develop in less than 72 hours.

Although a number of cases of acute cholecystitis will subside with conservative management, it is difficult to tell early in the attack what the course in an individual case will be. In 36 per cent of the 83 patients in our series seen early, initial conservative treatment failed and emergency surgical intervention became imperative.

Cholecystectomy performed early in the acute attack, after appropriate preparation, carries a significantly lower mortality rate than when performed later in the course of the attack. The relatively high mortality rate following cholecystectomy in patients operated on more than 72 hours after onset may be attributed to the more advanced and complicated forms of the disease. Of the 39 deaths occurring in our series, 19 (49 per cent) appeared to be due primarily to avoidable delay in operating. In 10 instances the delay occurred prior to hospitalization, and in 9 it occurred in the hospital. For these reasons we are convinced that patients with acute cholecystitis should be operated on as soon as they can be properly prepared.

Surgery of the biliary tract is technically exacting, particularly in the presence of acute cholecystitis. Inadvertent injury of the common duct results in prolonged disability and eventual death. For these reasons biliary surgery should be attempted only by those who are well qualified both in technical skill and in clinical judgment.

In the presence of acute cholecystitis, cholecystectomy—with choledochostomy if indicated—is the procedure of choice and can usually be performed safely. If the patient's condition is poor, cholecystostomy, under local and intercostal block anesthesia, may be preferable. A transverse incision is made 2 cm. below the palpable gallbladder, or the point of maximum tenderness. The fundus of the gallbladder is exposed and evacuated with a trochar. It is opened and the stones are removed; a Pezzer catheter is then placed in the fundus for drainage. This procedure not only provides relief in the acute attack but is often lifesaving. Since symptoms will persist or recur in about one-third of the cases, a secondary operation will be necessary at a later date.

If cholecystectomy is planned but severe

inflammatory changes in the hilum render such a procedure unduly hazardous, cholecystostomy may again be performed, or a more definitive type of partial cholecystectomy may be done. This procedure consists of excision of the gallbladder to the gallbladder bed and to the cystic duct. The mucosa remaining on the bed of the gallbladder may then be excised surgically or it may be thoroughly cauterized, and a drain placed down to the end of the cystic duct. In this manner the gallbladder is destroyed without the danger of injury to the common or hepatic ducts.

Summary

Acute cholecystitis is a common, serious disease of the biliary tract. The severity of the attacks and the case fatality rates increase with age. Acute attacks are usually preceded by recognizable chronic symptoms, and dangerous acute cholecystitis may be largely prevented by performance of cholecystectomy when stones are first discovered, particularly if symptomatic.

In the presence of an established attack of acute cholecystitis the patient should be surgically prepared and operated on promptly. Cholecystectomy is the procedure of choice but cholecystostomy or partial cholecystectomy may be indicated under special circumstances. Biliary surgery requires sound judgment and technical skill of a high order if disabling and fatal injuries to the vital biliary structures are to be prevented.

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OCHSNER CLINIC BUILDING

The "Frozen Shoulder"

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Are you aware of the various medical conditions predisposing to the syndrome of "frozen shoulder"? Are you employing the simple conservative measures that effect the cure of this frequent condition?

THOMAS DUNCAN

PAINFUL loss of motion in the shoulder joint (scapulohumeral joint) frequently occurs in persons of middle or elderly age who do not use the joint. This condition, commonly known as the "frozen shoulder," is also called adhesive capsulitis or adhesive periarthritis. All too often it develops in patients who are being actively treated for some other disease. Fortunately, if anticipated, it can be prevented or can be identified and satisfactorily corrected by simple conservative measures in most cases.

Adhesive capsulitis is frequently seen in patients suffering from cardiac or pulmonary disease, fractures of the forearm, subdeltoid bursitis, cervical arthritis or herniation of a cervical intervertebral disk. Pain referred to the shoulder, as in cases of cervical arthritis, or pain arising in the shoulder region, as in subacromial bursitis, will cause the patient to stop using the shoulder joint or initiate the syndrome, which will persist long after the inciting condition has become asymptomatic. Frozen shoulder motion often quickly develops in the patient who has recently had a coronary infarct and is afraid to move for fear he will die. Similarly, disability develops in the shoulder of the middle-aged woman with a Colles fracture, well reduced and held in a plaster cast, when she carries her arm in a sling for a few weeks and fails to use her shoulder. The syndrome is more often encountered in women than in men.

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Clinical Manifestations

In the early stages of the disease the shoulder is painful and feels stiff. The pain is variously experienced in the region of the greater tuberosity of the humerus, along the tendon of the long head of the biceps or at the insertion of the deltoid laterally in the upper third of the arm. It is felt on pressure over the shoulder or on motion of the joint. The motions of abduction, elevation and internal rotation are particularly aggravating. Pain is experienced when the patient tries to fasten clothing, particularly in the back, when reaching up to overhead shelves, and when combing the hair. The pain experienced at the deltoid insertion is referred pain and there is no associated local tenderness at the insertion. Occasionally the hand, arm, forearm, top of shoulder and lower cervical region may be painful as well. Sleep is frequently interrupted by severe pain.

Unless corrective measures are instituted, the symptoms become gradually worse. The range of motion in the shoulder joint that can be performed without causing pain becomes less and less until finally only a jot of motion or not even that remains; the arm is maintained at the side and the patient is extremely disabled. The forearm is maintained across the body, and attempts to use the hand, supinate and pronate the forearm or use the elbow aggravate the pain in the shoulder. The muscles of the shoulder atrophy and the acromioclavicular joint becomes prominent.

The duration of symptoms is variable, as is the intensity. All degrees of loss of motion occur, with spontaneous recovery occurring at any point in the course of the disease. Most untreated patients remain disabled (Figure 1) for many months and then gradually the pain subsides and concomitant increase of motion is regained until complete recovery occurs or only slight permanent loss of motion remains. Occasionally symptoms persist for years.

FIGURE 1. Characteristic deformity produced by the "frozen shoulder." (Illustration, courtesy of Wertheim and Rovenstine.[2])

Pathology

Microscopically, when the muscular inactivity occurs, all the shoulder tissues become filled with serofibrinous exudate, and adhesions form within the muscles, in the fascia and in the synovial and capsular tissues. This is a low grade, chronic inflammatory process. There is severe edema of the tissues, degeneration of the collagenous tissue with round cell infiltration, increased numbers of blood vessels, swelling of the synovial tissue and fibrosis.[1]

Treatment

Treatment consists first of correction of the inciting condition if still present, such as use of traction and cervical collar in cases of cervical arthritis, roentgen therapy for calcareous supraspinatus tendinitis or surgical excision of the calcareous material. Mild cases can usually be relieved by pendulum exercises and assistive shoulder exercises together with massage of the shoulder and application of heat. Blocks of the suprascapular nerve and the cervical sympathetic ganglions with procaine relieve much of the pain in the shoulder and are thus helpful in getting the patient started on the exercise program. Prolonged effect of the blocks can be obtained by adding DOLAMINE® to the procaine. The effect may last one or more weeks. The patient exercises within the limits of pain and tries to increase the range of motion. Pain continues as long as limitation of motion remains.

In severe cases the patient is placed in bed with the arm maintained in skin traction, sedatives are given freely, heat is applied to the shoulder and the nerves are blocked. The patient is instructed to try to exercise the arm some in the traction, rotating the shoulder. If possible a physical therapist should direct the exercises twice a day. When the arm can be abducted some from the side, the patient is allowed up and about and is made to do the pendulum exercises every 15 to 20 minutes all through the day and use the traction apparatus at night. Gradually, "walking up the wall" with the fingertips and exercises with an overhead pulley and rope are added. The arm is moved to maximum range and then an attempt is made to increase this range by having the patient tug on the rope and pull with the other arm. It is important to arouse the determination and enthusiasm of the patient whenever possible. The patient must be warned he cannot sit back apathetically and be

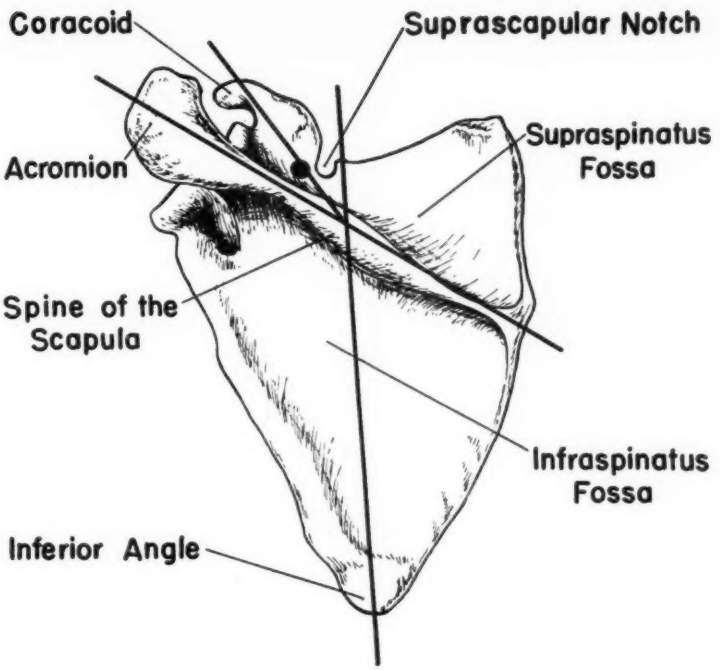

FIGURE 2. Diagram for blocking suprascapular nerve. Technic of suprascapular nerve block.

cured by the physician's ministrations.

Patients not requiring traction can be adequately treated and followed in the office. Patients requiring traction are best hospitalized at least initially. Suprascapular nerve block[2] is a simple procedure which may be safely performed in the office. However, because of the occasional complications following stellate ganglion blocks, it is preferable to do stellate blocks in the hospital.

The suprascapular nerve is the most lateral branch coming off the brachial plexus. It passes to the suprascapular notch at the root of the coracoid process, where it passes under the transverse scapular ligament and on the dorsum of the scapular process, and passes with the suprascapular artery across the supraspinatus fossa through the spinoglenoid notch to the infraspinous fossa supplying the supraspinatus and infraspinatus muscles and sending twigs to the shoulder joint.

Technic of suprascapular nerve block (Figure 2)—With the patient in a humped sitting position and the arms at the side, the inferior angle of the scapula is identified and marked on the skin, as are the medial and lateral ends of the spine of the scapula. A line is projected from the inferior angle of the scapula through the midpoint of the line of the scapular spinous process. The upper outer angle made by these two lines is then bisected and under sterile precautions a skin wheal is raised 1.5 cm. outward with a 2 per cent solution of procaine hydrochloride. A 22 gauge needle is pushed downward and medially until it strikes the scapula, when it is withdrawn and redirected slightly upward and inward 1 cm. further until it hits the suprascapular notch. Paresthesias are usually noted in the shoulder or arm at this stage. The plunger is withdrawn slightly to be certain blood has not been aspirated; then 8 to 10 cc. of the procaine solution is deposited. Preferably, 3 cc. is deposited followed by 10 cc. of dolamine, as this gives a much more prolonged action. Dolamine is nontoxic and contains 0.75 per cent ammonium sulfate. The ammonium ion obliterates C fiber potentials when injected into a nerve trunk; this action relieves pain but has no effect on cutaneous sensation or motor components. Dolamine has been shown to relieve pain effectively for a few hours to

4 or more days. Furthermore, frequently the second time dolamine is administered results last longer than after the first injection.

Stellate sympathetic ganglion block—Stellate sympathetic block with procaine hydrochloride[3,4] increases the pulsation, improves the circulation to the shoulder, improves the tissue oxygenation and increases the lymph flow. Compared with suprascapular block it is a much more hazardous procedure and therefore should not be done in the office.

Stellate block is not without complications. Subarachnoid injection is fatal. Procaine reaction rarely occurs but is serious. Treatment of this reaction consists of intravenous injection of barbiturates and administration of oxygen. Pneumothorax, phrenic nerve block, recurrent laryngeal block, hematomas and psychic reactions are other complications which may occur.

Corticotropin (ACTH) and cortisone are useful adjuncts in the treatment of the frozen shoulder. By helping to relieve the pain, they allow the patient to embark on the intensive exercise program. In addition, the associated euphoria is a stimulant to the patient's enthusiasm to cure his condition. These drugs are especially useful early in the treatment program. Both drugs should be given in small doses over short periods in order to reduce the possibility of development of untoward reactions. For example, Coventry[5] advocated daily intramuscular injections of 100 mg. of cortisone acetate for 5 days. If complete improvement is not obtained, treatment should be continued another 5 days. If further improvement is noted, 50 mg. can be injected intramuscularly each day for another 5 to 10 days. If no improvement is noted after the first 5 injections, use of cortisone should be discontinued and another form of therapy instituted.

Another recently introduced adjunct to treatment is phenylbutazone (BUTAZOLIDIN®). The dosage is 200 mg. 3 times a day at meals for 4 days. If the pain and range of motion are not significantly improved, a fourth dose is given at night, so that the daily dosage is 800 mg. Although this drug is still too new for accurate evaluation, it offers some promise. Its toxicity, however, may be a contraindication.

Manipulative treatment is almost never indicated. We have given up forcible manipulation of the "frozen shoulder" under general anesthesia. In rare cases when there is a single adhesion that gives way, manipulation is beneficial. However, it is most difficult to select such patients. In almost all cases many adhesions are felt to give way, and the capsular tissue, tendinous insertions and musculature are considerably traumatized. Following manipulations the patient has severe pain for several days, with swelling of the shoulder tissue. He is unable to move the joint and the usual result is that the adhesions recur often, so that there is more limitation of motion than prior to manipulation. Manipulation is therefore a dangerous procedure which cannot be recommended.

In selected long-standing cases operative treatment may be beneficial. This does not fall within the scope of this paper and will not be discussed.

Summary

The "frozen shoulder" is a frequently unrecognized condition caused by failure to use the muscles of the shoulder. It occurs in middle-aged and elderly persons, particularly women. The condition is characterized by pain in the shoulder with limitation of abduction, rotation and motion of the glenohumeral joint. Treatment is directed toward control of pain and return of motion. In most cases this can be accomplished by conservative measures.

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Gallstones: A Menace in Cholecystic Disease

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Gallstones represent a real hazard in acute cholecystic disease because of the possibility of the development of such dangerous complications as acute cholecystitis, obstruction of the common duct, choledochitis, intestinal obstruction due to gallstones, acute and chronic pancreatitis and carcinoma of the gallbladder. Therefore, every patient with gallstones should have them removed, whether or not they are producing symptoms, provided there are no contraindications to operation.

ALTON OCHSNER

BECAUSE cholecystectomy frequently fails to relieve the symptoms of noncalculous cholecystitis, this operation is being performed much less frequently now than previously. Although the hazards of cholecystectomy are potentially greater than those of many of the more commonly performed operations because of the possibility of injury to the extrahepatic ducts, a properly performed cholecystectomy is actually associated with minimal risk. However, unless there is a reasonable chance that the patient will be benefited by the operation, it is not justified, in spite of the minimal risk. Because many patients with noncalculous cholecystitis continue to have symptoms following removal of the gallbladder, many physicians, particularly internists, whose care these unfortunate individuals seek after an unsuccessful operation, become convinced that cholecystectomy should be performed infrequently. It is indeed understandable that internists should develop this philosophy since they see largely the bad results from the unsuccessful operative procedures.

Because noncalculous cholecystitis is seldom, if ever, complicated by conditions which jeopardize the patient's life, surgical treatment is rarely urgent, particularly if the symptoms can be adequately controlled by nonoperative measures. Although internists are more likely to advise conservatism in the treatment of cholecystic disease, surgeons are convinced that many of these patients should be subjected to operative intervention. This is particularly true in patients with associated cholelithiasis. In support of their conservative attitude, internists point out that many times gallstones are found at autopsy in individuals who had few or no clinical manifestations of their existence. Whereas this is not infrequently true, it is our conviction that regardless of whether they produce symptoms or not, gallstones represent a real menace because of the complications that can develop.

No physician would hesitate to recommend cholecystectomy to the patient with cholecystitis and cholelithiasis who has attacks of abdominal colic. On the other hand, many surgeons as well as internists might be reluctant to advocate cholecystectomy in a pa-

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tient with asymptomatic cholelithiasis. It is because of the possible complications of gallstones that we firmly believe that all patients with biliary concretions should be operated on unless the procedure is definitely contraindicated. Possible dangerous complications include acute cholecystitis, obstruction of the common duct, choledochitis, intestinal obstruction due to gallstones, acute and chronic pancreatitis, and carcinoma of the gallbladder. The dictum that operation is indicated in all patients with gallstones may seem dogmatic and radical, but considerable experience in the management of many patients with these complications has convinced us that it is correct. Naturally, internists would be less likely than surgeons to appreciate the hazards of gallstones, because they seldom see patients with complications resulting from gallstones. This, together with the fact that they are more likely to see the individuals who have not been benefited by cholecystectomy for noncalculous disease, is responsible for their belief that cholecystectomy is rarely indicated.

The incidence of gallstones in patients with cholecystitis is difficult to determine. Mayo[1] estimated that 70 per cent of patients with cholecystic disease have stones. Biliary concretions are common in adults. In 600 consecutive necropsies on adults at the Mayo Clinic Mentzer[2] found 21 per cent with gallstones. In a necropsy study at the Johns Hopkins Hospital of 1,655 individuals dying in the fourth decade of life, Mosher[3] found 8 per cent with gallstones. Crump[4] reported the incidence of gallstones to be 32.5 per cent of 1000 necropsies and 50 per cent after the seventh decade of life. Robertson and Dochat[5] found gallstones in 16.2 per cent of men and 37.1 per cent of women past the age of 40 years in a series of 16,936 autopsies.

Graham and Mackey[6] have shown that approximately 40 per cent of patients with cholecystitis without calculi will be cured spontaneously of dyspepsia which is not associated with pain. A patient with noncalculous cholecystitis frequently complains of discomfort after eating and qualitative dyspepsia. However, the clinical manifestations are seldom if ever as severe as they are in those with calculi. Gallstone colic, particularly if a calculus has passed through the cystic and common ducts, is severe. However, the severity of these symptoms cannot be compared with the seriousness of the complications which may be produced by calculi.

It is the consensus among clinicians that *acute cholecystitis* is, with few exceptions, produced by gallstones. In a series of 468 consecutive cases of acute cholecystitis observed at the Charity Hospital in New Orleans during the 11 year period ending June 30, 1951, stones were absent in only 7 per cent of cases. In many cases, if not most, these stones probably had been present but had been passed before the gallbladder was removed. It is impossible to determine the incidence of acute cholecystitis in patients with calculous disease of the gallbladder, but every patient with gallstones represents an individual in whom acute cholecystitis can develop.

In contradistinction to chronic cholecystitis with or without calculus in which surgical therapy is attended with little risk, the danger of acute cholecystitis is considerable. In the series of 468 cases from Charity Hospital there were 39 deaths, a case fatality rate of 8.3 per cent as compared with a mortality rate of less than 1 per cent following cholecystectomy for uncomplicated cholecystitis. The risk in acute cholecystitis, however, is dependent on many factors. For one thing the disease is usually more severe in older persons than in younger people. Whereas only approximately 30 per cent of patients with acute cholecystitis less than 40 years old had a severe process, in 38 per cent of the 40 to 59 year age group and in 56 per cent of the 60 year age group the process was severe (Figure 1). Moreover, in 134 cases of patients under 40 years of age, there were no deaths, but 11 deaths occurred in 201 patients between 40 and 60 (5.5 per cent) and 28 deaths among 133 patients aged 60 years or over (21.1 per cent).

It is thus evident that acute cholecystitis is a dangerous condition, particularly in older individuals. Although there may be greater hesitation in advising operation for gallstones in older individuals because of the presumably

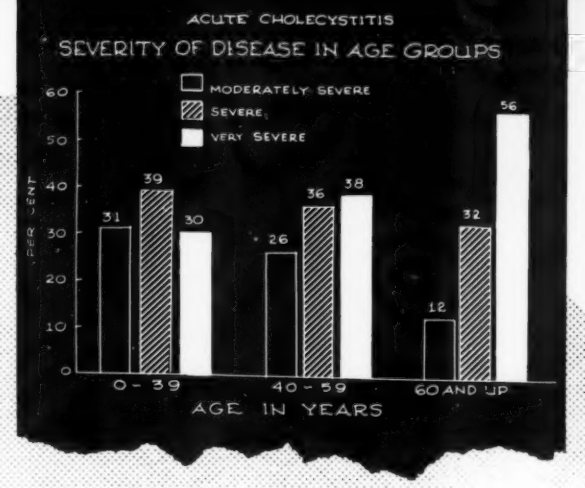

FIGURE 1. Distribution of cases of acute cholecystitis in different age groups according to severity of the disease. (Courtesy of DeCamp, P. T., et al.: Timing in the surgical treatment of acute cholecystitis. Ann. Surg. 135:734-750 [May] 1952.)

greater surgical risk of such individuals, the risk is even greater if the patient retains the gallstones with the possibility of the development of acute cholecystitis at an advanced age. We, therefore, believe that cholecystectomy for gallstones is even more essential in an individual past 50 years of age than in a young person.

Although most physicians believe that small gallstones represent a hazard because they can pass through the cystic duct into the common duct and produce complications such as jaundice, choledochitis and cholangitis, many have the fallacious concept that large stones, and particularly solitary ones, are not dangerous because of the misconception that such calculi cannot produce obstruction. Because of the conical shape of the gallbladder, a calculus, unless it completely fills the gallbladder, can slip down and produce obstruction of the gallbladder at the point where it becomes incarcerated. Also, it is the large and usually solitary stone which, by virtue of its weight, can cause the gallbladder to descend into the region of the duodenum and by pressure set up a localized area of inflammation, producing agglutination between the adjacent portions of the gallbladder and the duodenum and ultimately erosion of the gallstone through the gallbladder and the duodenal walls into the lumen of the duodenum with production of spontaneous choledochoduodenostomy. In such an instance, the large stone passes into the duodenum, is transported through the

small intestine by peristaltic motion and usually becomes incarcerated in the terminal ileum, which is the narrowest part of the small intestine, causing acute gallstone ileus. Unless the condition is recognized early and the stone removed before irreparable damage occurs to the ileum at the point of incarceration, perforation with peritonitis results. Although at present the mortality rate in gallstone ileus is not as high as it was before the availability of antibiotics, it is still a hazardous condition which is preventable as is cholecystoduodenostomy by removal of the gallbladder and the gallstones before perforation has occurred.

There is always danger of gallstones in the gallbladder obstructing the cystic duct with production of acute cholecystitis or empyema of the gallbladder or of passing through the cystic duct into the common duct. The frequency with which stones pass from the cystic into the common duct is difficult to determine but undoubtedly this occurs much more commonly than is known. Probably in most individuals with gallstones who have gallstone colic, the stones pass into and through the common duct into the duodenum. In a series of 13,343 patients operated on for gallstones, Judd and Marshall[7] found stones in the common or hepatic ducts in 1,768 cases (13.2 per cent). In the Charity Hospital cases of acute cholecystitis, there were 425 with cholelithiasis and 53 with associated choledocholithiasis (12.4 per cent). The presence of gallstones in the common duct does not necessarily mean obstruction of the duct, because undoubtedly in many instances a stone gains entrance to the common duct and is passed through the ampulla of Vater without producing obstruction. A stone may remain for some time in the common duct and produce temporary obstruction from time to time—not long enough to cause jaundice but enough to produce recurrent attacks of colic. McKittrick and Wilson[8] found that jaundice was present in only 55 per cent of their patients with common duct stones.

Choledochitis producing obstruction of the common duct with resulting jaundice and stasis in the liver increases the risk of the condition. There is less danger of obstructive jaundice at the present time than previously, because unless the condition has existed for some time with resultant hepatic damage, hemorrhagic tendency due to hypoprothrombinemia caused by lack of bile in the intestine can be corrected by the administration of vitamin K. Because of biliary stasis, cholangitis, both nonsuppurative and suppurative, can occur as a result of obstruction of the common duct. In such an instance, active antibiotic therapy preoperatively is essential but prolonged delay of operation may be hazardous.

As originally noted by Opie,[9] obstruction of the ampulla of Vater by a calculus in an individual in whom the duct of Wirsung opens into the common duct above the ampulla permits regurgitation of obstructed bile into the pancreatic duct with the production of acute pancreatitis. Although this undoubtedly is not the only cause of acute pancreatitis, it is probably the most frequent, as has been emphasized repeatedly by Gage.[10] Pancreatitis, even though now treated quite satisfactorily by conservative measures—particularly vasodilation produced by splanchnic block—is a dangerous condition which should be prevented if at all possible. It can be prevented in most instances by removal of the gallbladder and the gallstones before a stone becomes incarcerated in the ampulla. In addition to acute pancreatitis, chronic and relapsing pancreatitis can be caused by common duct stones, and they too can be prevented by early removal of gallstones.

Of all the complications of gallstones, cancer of the gallbladder is undoubtedly the most dreaded, because once the condition has progressed so that it can be suspected or diagnosed clinically, nothing can be done in a curative way. The intimate lymphatic connections between the gallbladder and the liver preclude complete removal of the lesion once extension has occurred. Cancer of the gallbladder occurs much more commonly than is generally thought. In a series of 2,314 cases observed at autopsy by von Berencsy and von Wolff,[11] carcinoma of the gallbladder was found in 2.77 per cent of men and 10.7 per

cent of women. Graham[12] estimated that carcinoma of the gallbladder represents between 8 and 10 per cent of all cancers and its incidence is about 9 per 100,000 for the general population.

Carcinoma of the gallbladder probably never occurs without the presence of gallstones. Siegert[13] found calculi in 94 of 99 patients with carcinoma of the gallbladder. It is difficult to say in what percentage of individuals with cholelithiasis carcinoma of the gallbladder will develop. Lentze[14] found carcinoma of the gallbladder in 5.1 per cent of a series of 557 women 40 years of age and older with cholelithiasis. Graham[15] stated that at Barnes Hospital 8.5 per cent of patients with cholelithiasis had associated carcinoma of the gallbladder. He believes that carcinoma of the gallbladder will develop in 4 to 5 per cent of all women in the cancer age who have gallstones unless the gallbladder is removed. In a series of 468 cases of acute cholecystitis observed at the Charity Hospital, adenocarcinoma was found incidentally, although limited to the gallbladder, in 6 cases (1.3 per cent).

Carcinoma of the gallbladder is almost entirely preventable, because most if not all cases are the result of persistence of gallstones in the gallbladder. Although the risk of developing carcinoma in the presence of gallstones may not be particularly great, possibly between 2 and 5 per cent, the danger of cholecystectomy for uncomplicated cholecystitis and cholelithiasis is much less than this. According to Graham[15] the risk from operation in uncomplicated cholelithiasis is about one-fourth or one-fifth the danger of death from carcinoma of the gallbladder. He estimated that "one person in about 25 with gallstones will have a carcinoma of the gallbladder."

It is evident from this discussion that gallstones present a real hazard, and although the patient harboring the stones may or may not have symptoms, he should be operated on unless there is a contraindication to an operative procedure. At times the diagnosis of gallstones may be difficult, particularly in the presence of a nonfunctioning gallbladder. Only approximately 30 per cent of biliary calculi have sufficient calcium in them to cast a shadow in the plain roentgenogram. In those cases in which there is sufficient function in the gallbladder so that it can be visualized, nonopaque stones are visible as negative shadows. Frequently, however, individuals with biliary calculi have severe enough cholecystic disease so that the function of the gallbladder is insufficient to permit visualization. In these instances, the diagnosis of cholelithiasis must be made from the symptoms alone. A diagnosis of cholelithiasis is justified in any patient who has recurrent attacks of biliary colic associated with a nonfunctioning gallbladder, and operation is indicated. If there is any possibility at all of the presence of calculi, the gallbladder and its contained calculi should be removed unless there is some definite contraindication to the procedure, because only in this way can the possibility of the development of complications, which are responsible for most of the deaths in patients with cholelithiasis, be minimized.

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Carcinoma of the Prostate

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The common occurrence of carcinoma of the prostate is not fully appreciated. Radical excision offers a possibility of cure if the disease is discovered in its early stages, when it is clinically recognizable in most instances. Moreover, palliative therapy, in the form of hormones or irradiation, has proved successful in controlling symptoms and retarding progress of the disease in inoperable cases.

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THE total incidence of occult as well as clinical carcinoma of the prostate in men past 50 years of age is remarkably high, a fact which is probably not yet fully appreciated by most of the medical profession. Incidences as high as 29 per cent in routine autopsies of old men appear frequently in the literature, and even though many of these are occult in nature, the potential threat of clinical carcinoma of the prostate has been shown to be present in nearly one-third of the male population past 50 years of age. This would mean that at the present time between 3,000,000 and 5,000,000 men in the United States have cancer of the prostate. Cancer is the cause of approximately one-fifth of the cases of prostatic obstruction encountered clinically.

Etiology

No correlation has ever been demonstrated between carcinoma and other lesions of the prostate. Cancer frequently occurs in association with benign prostatic hypertrophy but there appears to be no inner relationship between the two lesions. Cancer will occur just as frequently in otherwise normal glands. Chronic inflammatory prostatitis has never been shown to be a precursor of carcinoma. Also there appears to be no relationship between the relative degree of previous sexual activity and the development of subsequent carcinoma. It usually is encountered in men past the age of 50 years, with the highest incidence in those between the ages of 55 and 85 years, although isolated cases have been reported in men in the third and fourth decades of life. Prostatic cancer has never been known to occur in eunuchs.

Pathology

Whereas cancer may originate in any portion of the prostate, it occurs with greatest frequency in the posterior and lateral lobes of the gland. Moore[1] reported that 73 per cent arose in the posterior lobe, 9 per cent in one lateral lobe and 16 per cent in the anterior aspect of the gland.

Carcinoma of the prostate, in contrast to

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benign prostatic hypertrophy, usually originates in the periphery of the gland, most often in its posterior aspect, in between 80 and 90 per cent of cases. This is highly significant for 2 reasons: (1) It makes the disease clinically recognizable by rectal palpation even in its earliest stages in the majority of cases, and (2) it explains the absence of early urethral symptoms since immediate obstruction to urination does not occur.

As the disease progresses, it extends throughout the substance of the prostate gland itself and infiltrates the capsule, seminal vesicles and later perineural lymphatics. The mass may or may not encroach on the urethral lumen, producing urinary obstruction. In the advanced stages it may also invade the trigone producing not only urinary obstruction in this fashion but also occlusion of the ureteral orifices with attendant symptoms of renal failure. Microscopically, most carcinomas of the prostate are adenocarcinomas. Some grow slowly and are difficult to recognize even microscopically in the early stages, whereas others are rapidly growing with highly malignant tendencies and extremely anaplastic microscopic characteristics. This latter type may be so fulminating in character at times as to simulate acute inflammatory disease of the gland and usually occurs in relatively younger men.

Metastases

Metastases occur via both the lymphatics and blood stream. They may appear early or late, depending on the inherent growth characteristics of the neoplastic cells in the primary lesion. In some instances gradual local extension into the seminal vesicles and other adjacent areas of the deep pelvis may continue for years without recognizable dissemination of the disease beyond the pelvis. When distant metastases occur, the bony pelvis and lumbar vertebras are favorite sites. In order of frequency the bony structures involved are the pelvis and sacrum, the lumbar spine, dorsal spine, cervical spine, femur, ribs, shoulder girdle, humerus and skull. When the perineural lymphatics are involved, the regional lymph nodes and lymphatic channels of the true pelvis will be most frequently involved.

Symptoms

Carcinoma of the prostate is a silent disease until symptoms of urinary obstruction or metastases occur. This is the chief reason for delay in diagnosis and consequently for the failure of cure in such a distressingly high percentage of cases. When symptoms do occur, they are most often those of frequent and difficult urination. In others, in whom obstruction to the prostatic urethra is minimal, even after long-continued progress of the disease, the symptoms will be due to the metastases. Pressure exerted by metastases on the nerves of the pelvis will cause localized pain in or near the rectum, the lower part of the abdomen or the perineum. Unilateral or bilateral sciatica is a not infrequent chief complaint of patients with carcinoma of the prostate, which may have progressed insidiously for years without producing urinary obstruction. Backache, pain in the leg and loss of weight are manifestations of advanced metastatic prostatic cancer involving the bony system. Other systemic symptoms, such as anemia, may occasionally be the predominant sign. Hematuria occurs less frequently than in benign prostatic hypertrophy. More rarely, metastases to visceral organs, such as the lungs or liver, may initiate the presenting symptoms.

Diagnosis

Since most of these lesions occur in the periphery of the gland, the disease is usually recognizable by simple rectal palpation of the prostatic capsule. It is to be hoped that the medical profession in general will become increasingly conscious of the importance of routine rectal examination of all men over 50 years of age. In early cases small areas of malignant change, even less than 1 cm. in diameter, can be readily recognized by the examining finger as an isolated, nodular, firm and well-defined area within the capsule. This should be considered as immediately suggestive of carcinoma of the prostate until proved otherwise, for it is in these cases alone that complete cure of the disease is possible. In

more advanced cases the tumor will have involved large portions of the gland producing an irregular and extremely firm palpable mass infiltrating the prostate itself with fixation of the gland and obliteration of its normal contours. It may extend on up to one or both seminal vesicles or laterally into the periprostatic areas obliterating the normal peripheral demarcation of the gland. The size of the prostate itself may or may not be materially affected. In some instances the mass becomes so large that an indentation into the rectum is produced, whereas in others the tumor grows toward the urethra and trigone so that there is little change in the size of the prostate on rectal palpation.

Whereas cancer will ultimately be found to be the etiology in most prostates presenting these findings on rectal palpation, several other prostatic lesions must be excluded. Chief among these is calculus, which can be readily excluded by means of a plain roentgenogram of this area. Tuberculosis of the prostate can be eliminated by the concomitant clinical findings, particularly the microscopic evidence in the urine and prostatic secretions, and the roentgenogram. Chronic inflammatory prostatitis may sometimes, particularly in long-standing cases, produce changes difficult to distinguish from cancer on mere rectal palpation. However, the history of long-standing infection plus the observation of considerable pus in the prostatic secretion will make an immediate diagnosis of cancer questionable. Repeated prostatic massages improve drainage of the involved acini in these cases so that the previously noted firm areas will become soft in a short time. Old healed infarcts of the prostate may occasionally be confused with cancer. In all suspected cases roentgenograms of the lumbar spine, pelvis and femurs should be made to exclude bony metastases. These may occasionally be found even when the presenting lesion on rectal palpation is small.

Determination of the serum acid phosphatase level has assumed an important place in the diagnosis of carcinoma of the prostate with metastasis. Acid phosphatase activity is high in the prostate gland itself, appearing at puberty. It is present in small amounts in normal human serum but greatly elevated in the serum of more than half of the patients with metastases. Although the level may be normal when metastases are present, it is not elevated when they are absent. Also, elevation of the serum alkaline phosphatase will occur in 90 per cent of patients with demonstrable bony metastases from cancer of the prostate. This enzyme occurs in many organs, but only that from bone appears in the blood stream in significant amounts. It appears whenever new bone forms as in fractures, Paget's disease or osseous tumors, and is therefore not pathognomonic of metastases from carcinoma of the prostate as is the case in the acid phosphatase level, since the latter comes only from the neoplastic cells themselves as they develop in areas beyond the prostate gland.

Biopsy, by removal of prostatic tissue with a needle inserted through the perineum, has been employed for many years with varying degrees of success and enthusiasm by those advocating its use. Its chief disadvantage is that it requires considerable practice in order to promise even a reasonable degree of success, and whereas positive results may be diagnostic, negative ones are meaningless.

Transurethral biopsy by means of prostatic resection is sometimes unreliable, since in many instances the tissue removed is not sufficiently near the periphery of the gland to yield positive results. This is so well recognized that in instances in which rectal palpation reveals the characteristic stony hardness, irregularity and fixation associated with carcinoma, the diagnosis of cancer is still considered clinically certain and the patient treated accordingly, despite the fact that tissue removed by transurethral resection may yield only benign elements.

Perineal biopsy, however, is the surest means by which prostatic cancer can be positively demonstrated in patients in whom a suspicious lesion is discovered on rectal palpation. The procedure itself is simple and entails little or no risk and slight morbidity, since the urinary tract is not opened. Because a positive diagnosis of the lesion by frozen section is often difficult, many have recently

adopted the practice of performing perineal biopsy and waiting for the final tissue report before proceeding with plans for radical prostatectomy in those instances in which the biopsy report is positive.

The diagnosis by microscopic demonstration of neoplastic cells in the expressed prostatic secretion by the method of Papanicolaou has not as yet been sufficiently developed to be considered a reliable diagnostic aid. Not only does this technic require special training and considerable experience, but also it is somewhat more difficult to differentiate those cells encountered in prostatic secretions than in some other body fluids. Moreover, absence of malignant cells in the specimen does not preclude the possibility of cancer, particularly as the majority of these lesions are in the periphery of the gland and therefore not capable of adequate drainage of their cells into the secretion on massage, especially in the equivocal early nodular lesions which are really the only ones in which any reasonable doubt of diagnosis exists in the first place.

Elevation of the sedimentation rate may or may not be an important corroborative sign, since it is not consistently present in all cases even when extensive metastases are present. Published reports vary from almost 100 per cent elevation[2,3] to 50 per cent.[4]

Treatment

Carcinoma of the prostate should be curable, as is cancer in any other part of the body. However, unfortunately, even today with our cancer-conscious population and increasing recognition of the importance of routine rectal examination in men over 50 years of age, only 5 to 10 per cent of cases of carcinoma of the prostate are recognized at a stage when complete extirpation is possible.

Of the 2 surgical approaches possible for radical prostatectomy, perineal or retropubic, the perineal is generally considered by most as preferable. This operation, which was first introduced by Hugh Young in 1906, is gradually being more widely accepted, particularly as a result of the impetus given to the technic by improvements introduced by Belt.[5,6] This approach to the gland permits first of all an opportunity for exposure and biopsy of suspicious nodules in the posterior capsule so that it is possible not only to determine accurately those requiring radical resection but also to spare those on which results of biopsy are negative. It permits easy and complete removal of all involved structures. The incidence of urinary incontinence by this method is now practically nil, and the operative mortality and morbidity compare favorably with those associated with subtotal prostatectomy by the other approaches. Continued experience with radical prostatectomy in recent years has led to the appearance of an increasing number of favorable reports.[6-11]

About half of those patients with early carcinoma of the prostate treated by radical perineal prostatectomy have been reported to survive 5 years without evidence of recurrence, as compared with an average reported 5 year survival rate of 10 per cent for untreated controls who had no metastases when first seen and 34.3 per cent for those subjected to all forms of palliative therapy.[12] It is to be hoped that an ever increasing number of early cases will be detected by routine rectal examinations when radical excision can offer definite hope of cure.

Palliative treatment of incurable carcinoma of the prostate consists (1) of relief of urinary obstruction when present, usually by transurethral resection or occasionally suprapubic cystotomy when resection is not feasible, and (2) of use of hormone therapy or irradiation in an effort to retard or control development of the local growth and its metastases.

Hormone therapy was given its greatest impetus by Huggins,[13] who in 1941 demonstrated the value of the female sex hormone in the control of this disease. Since then this form of therapy has been universally employed in incurable cases either by oral or parenteral introduction of the female sex hormone, or by castration, or by both. Whereas this form of therapy cannot produce a cure, present experience has shown not only spectacular and consistent increase in the life expectancy of almost all patients so treated, but also control of the symptoms and tem-

porary regression of the disease in most cases. In the largest single group of cases so far studied, Nesbit and Baum[12] reported that in those patients with inoperable carcinoma of the prostate treated either by oral administration of hormones or by orchiectomy or by a combination of these, a significantly greater number of patients in all categories were alive after 5 years than among untreated controls in whom from 90 to 94 per cent were dead at the end of 5 years. Most patients with inoperable carcinoma of the prostate treated by hormone therapy, even those with extensive metastatic disease, show clinical improvement. Elevated levels of serum acid phosphatase may return to normal and the size of the prostate may regress to such a degree that it is impossible to detect gross evidence of tumor on rectal palpation. These patients regain their strength, are relieved of metastatic pain and are able to resume an active life.

There is still some question in the minds of many students of this problem as to the exact method of employment of hormone therapy. Many of the questions involved can be finally answered only after additional years of observation of results. There is no certainty, for example, as to whether hormone therapy should be instituted in the absence of demonstrable metastases or systemic symptoms, whether it should be employed first without orchiectomy, or whether the two should be used together. Since it has been observed that a relapse following the use of one form of hormone therapy may be temporarily counteracted by the employment of the other, many prefer use of stilbestrol orally at first with orchiectomy held in reserve. Yet there is evidence that the combined use of both forms of therapy at the time of recognition of the disease may lead to a longer life expectancy in a large series of cases.[12]

The dosage of the female hormone to be used is also still a matter of some speculation. It was originally thought that only from 3 to 5 mg. of stilbestrol could be absorbed in 24 hours and that anything above this was in excess; yet clinical experience has shown that increasing the dose sometimes produces good results in patients not responding well to small doses. It is now a frequent practice to give daily doses of as much as 45 mg. or more, particularly in those with advanced disease who have not responded to small doses. There also appears to be suggestive evidence that the use of the hormone following orchiectomy may be of added value.

Aside from the use of estrogenic hormones in the control of prostatic cancer, it has become apparent that certain other hormones[14] may exert a beneficial influence on the primary tumor and metastases. Testosterone, and likewise progesterone, have been tried on the theory that they will cause a decrease in the formation of the androgen-stimulating hormone of the pituitary, and beneficial clinical effects have been noted following cessation of this therapy. In fact, symptomatic improvement in a small series of cases, even during administration of testosterone, has been reported. Cortisone is now being used in advanced cases of prostatic carcinoma which have proved refractory to female sex hormone therapy. It has proved to be of considerable value from the symptomatic standpoint in some cases. It is presently thought that cortisone should not be given until the beneficial effects following orchiectomy have been exhausted. The beneficial effects of cortisone are believed to be due to atrophy of the adrenal cortex, which cortisone causes. The drug is given in doses of 50 mg. daily and is usually combined with continued estrogenic therapy. In addition to relief of symptoms directly referable to the prostatic carcinoma, some euphoria and increased appetite are noted. Its use is contraindicated in patients with congestive heart failure, obvious psychoses, tuberculosis, peptic ulcer, diabetes and renal insufficiency.

Bilateral total adrenalectomy, as described by Huggins,[15-17] has been employed with success in some cases of advanced carcinoma of the prostate which have escaped from the effect of androgen suppression, either by estrogen administration or by orchiectomy. In the early cases the patients subjected to adrenalectomy died because of inability to handle adequately the hormonal and electrolyte problem created by removal of the ad-

renal cortex, but since the advent of cortisone and the greater accumulation of knowledge concerning adrenocortical activity, it has become possible to remove both adrenals safely with the expectation of being able to supply the necessary factors needed for survival. This procedure is being more and more frequently employed in carefully selected cases of advanced carcinoma of the prostate no longer responding to androgen suppression with the hope of being able to remove completely the extragonadal source of androgenic hormones. The results so far are encouraging and the final evaluation of the end results will be awaited with great interest.

Irradiation therapy, in the form of deep roentgen rays or radium, has never proved very effective and is of only limited value. Occasionally roentgen ray therapy may influence metastatic lesions to an extent sufficient to increase the comfort and well-being of the patient or to prevent sloughing or bleeding from the local lesion, but it is impossible to deliver an effective dosage to the primary tumor itself without serious damage to neighboring structures. Radium has proved of questionable value because of the local reaction that it may produce in the immediate area with distressing postirradiation symptoms. More recently, the injection of radioactive gold isotopes directly into the prostate and vesicles through a combined suprapubic and retropubic approach has given promise of success in controlling temporarily at least the localized lesion. This form of therapy is currently being tried only in those patients with inoperable carcinoma but no evidence of distant metastases, and the final results of such therapy remain to be determined. The preparations presently used contain 90 per cent beta rays of about 3 mm. range, which fact minimizes the chance of significant adverse reaction in adjacent structures. Its local diffusion through the growth after injection is aided by the inclusion of hyaluronidase. Its total effective action continues for 1½ weeks with its half-life of 2.7 days, and most of it remains in the prostatic area with a fraction lost in the urine but only an insignificant amount through the blood stream.

In conclusion, it should be emphasized that whereas several forms of palliative therapy have proved successful in controlling symptoms and retarding the progress of prostatic carcinoma for many months or years, it is still imperative, as in cancer in any other part of the body, to recognize the disease while it remains localized so that it may be radically extirpated.

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Gout — Its Diagnosis and Treatment

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Gout has become the forgotten disease, seldom recognized though rather prevalent. Early recognition and prompt treatment can prevent articular and renal damage. Colchicine remains the most specific drug for the relief of acute attacks and the most valuable in the prophylactic management between attacks, but several newer agents are proving their therapeutic worth as adjunctive measures.

GOUT is usually manifested clinically by acute articular symptoms, then chronic progressive articular disability with residual limitation of the movement of the joints and possibly renal damage. Although thought to be rare, the disease will be commonly encountered if one looks for it. Unfortunately, it is a seldom-remembered malady[1-4] despite the unchanging clinical picture, the usual typical pattern of each attack, the relief that can be obtained, and the articular and renal damage which may be prevented by early recognition and proper medical care. The painful joint or joints presented by the patient with gout are usually identified simply as "arthritis" or "rheumatism," and general nonspecific measures are recommended throughout the natural course of the attack. Such measures are often credited with alleviating these spontaneously subsiding attacks, and usually the condition remains undiagnosed until attacks become so frequent, severe or disabling that special studies are done. When diagnosed early, proper treatment affords gratifying results to both the patient and his physician.

The etiology of gout remains unknown. In recent years attention has been directed toward the role of body synthesis of uric acid from simple molecules that are available in the body.[5,6] The amino acid glycine may be more rapidly converted to uric acid in the patient with gout than in the normal person.[7] It has also been suggested that an abnormal androgen is formed in these patients.[8]

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Diagnosis

Recognition of gout depends not only on knowledge of its clinical features but also on continued awareness of its frequent occurrence. It therefore seems of value to review the typical pattern of this disease, for only by familiarity with these clinical characteris-

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tics can we arrive at a specific diagnosis of gout rather than the general one of arthritis.

The patient with an acute attack of gout in a weight-bearing joint is either unable to walk because of pain or walks awkwardly with a great deal of effort, using a cane or a crutch and carefully guarding the involved joint and avoiding any pressure on it. The patient is probably a man, for approximately 95 per cent of cases occur in men. Usually overweight, bald, ruddy and jovial, the male patient with gout is around 40 years of age but may be as young as 18 years or in his late years. When gout occurs in a woman, she has usually already undergone the menopause. In women the disease follows about the same pattern as in men, but in our experience the initial attack does not usually occur in women with the suddenness or severity that is common in men.

The acute attack begins with unusual suddenness, perhaps awakening the patient in the early morning hours, although he probably was feeling fine when he went to bed. Whereas many attacks do begin in the early morning hours, they can occur at any hour. If it is the first attack, the patient complains that he has never before experienced anything as painful. Thus, the pain of gout is usually described in expressions of intensity rather than of type. One patient mentioned that he "could not tolerate the weight of a cigaret paper on the joint" and another recalled that he feared a fly which was in his room would land on the involved toe. The pain is most often described as a bursting or boring pressure. A sudden knifelike pain which lasts only a few minutes is more characteristic of acute rheumatoid arthritis.

The pain of acute gout reaches its maximum intensity in a matter of a few hours and lasts several hours or several days. So intense is the pain that the patient is unable to bear weight on the involved part and welcomes use of a crutch or a cane. If the great toe is the site of involvement, the patient does not hesitate to *cut* his foot gear to prevent pressure on the inflamed part. On the other hand, the patient with chronic arthritis, such as rheumatoid arthritis, will not feel the urgent need of cutting his shoe but instead has time to obtain larger foot gear. It has been said that a middle-aged man with acute arthritis who comes into the physician's office wearing a split shoe and using a cane must be considered to have gout until proved otherwise.

Failure to realize that in gout any joint in the body can be affected often delays the diagnosis. The first metatarsophalangeal joint of either or both feet is eventually involved in 80 to 90 per cent of patients with acute attacks, but the initial attack may find this joint affected in only about 60 per cent of cases. Patients with gout frequently have olecranon bursitis which, when present, means that a diagnosis of gout is warranted. If rheumatoid arthritis is present, this bursa may be prominent, but it will usually contain pea-sized nodules that can be removed and studied microscopically if the diagnosis is in doubt. In patients with gout the knees, wrists, ankles and thumbs are often the site of acute arthritis. The hips, spine, shoulders and temporomandibular joints are rarely involved in patients with gout.

In about 95 per cent of the cases of acute gout only one joint is affected. Polyarticular involvement occurs usually in younger patients. Because of the frequency of attacks involving the great toe, the remainder of the foot is often ignored as a possible site for acute gout. Any portion of the foot may be involved, presenting a picture of cellulitis requiring surgical incision.

The involved joint is swollen, red or bluish red, and shiny with adjoining edema. Motion of the joint is avoided, and the patient usually discourages palpation of the foot, which is hot, dry and firm compared with the cold, clammy, bluish white and soft joint of rheumatoid arthritis. Desquamation occasionally follows subsidence of the acute articular swelling.

The temperature may be elevated, though fever above 102° F. is uncommon. Except for the articular pain these patients feel well. Seldom do they complain of fatigue, lassitude or general malaise as in rheumatoid arthritis.

Fortunately, most acute attacks of gout last no longer than 7 to 14 days. The swelling,

pain and tenderness subside and recovery is complete in the majority of cases. Rarely, a joint may remain swollen, red and tender for months. The fact that recovery is complete and the former site of involvement is subjectively and objectively well and shows no residual strongly favors a diagnosis of gout. When questioned closely, the patient with rheumatoid arthritis will relate that the joint formerly involved "is not quite as good as before, but at least it is much better," whereas the patient with gout will say without hesitation that the joint is completely well.

Inquiry into the patient's past history may furnish pertinent information. A family history of gout has been emphasized in Great Britain, although it has not been as commonly noted in this country. The history of renal calculi in the family or patient is also a clue suggesting an elevated uric acid level. Uric acid stones or gravel is noted in about 11 per cent of patients with gout.

It is not known why acute attacks of gout occur in the spring and fall. The history of an attack while on a trip, attending a convention or fishing or hunting, suggests the disease. Mild trauma, such as caused by an unaccustomed long walk or using a garden spade, may precipitate an attack in a susceptible individual. In the differentiation of an acute gouty joint from one that has been significantly traumatized, it should be appreciated that in gout symptoms will develop later than they will after an injury. Also, in gout the symptoms are out of proportion to the amount of trauma, and the area of discomfort and swelling may progress rather than localize.

Although the direct association of gout with exogenous purine is not known, in some individuals dietary indiscretion seems to play a significant predisposing role. Not infrequently acute attacks develop after some celebration, banquet or holiday. Only an occasional patient can precipitate an acute attack of gout by indulging in one or more specific foods of high purine content. Usually the diet of the average patient is devoid of excessive canned fish, liver, brains and sweetbreads. Meat, thick gravies and condiments are more popular with these patients. Alcohol has been considered a precipitating agent though this has never been proved.

An acute attack of arthritis appearing from several hours to 9 days after a surgical procedure should be considered gout. Injections of liver extract, mercurial diuretics, insulin, GYNERGEN® and possibly vitamin B may precipitate an acute attack. Administration of ACTH followed by withdrawal may also initiate an acute episode. Rapid loss of weight may be a provoking factor.

Although during the acute attack of gout tension, apprehension, depression and irritability are common, emotional factors do not play a role in precipitating attacks of gout, which is a point of differentiation from rheumatoid arthritis.

The longitudinal pattern of gout is also a valuable diagnostic aid. Some patients will have recurrent attacks about 18 months apart. Others may never have more than one attack. Still others have more than one attack at irregular intervals and with no residual. Finally, some may have numerous attacks that tend to appear more frequently, last longer and show signs of decreased articular efficiency. Early in the course of the disease the periods between attacks are devoid of any subjective residual signs and the patient feels fine. Rarely does a case become chronic from the onset.

After a patient has experienced several attacks, he may be able to detect when an attack will occur. Often, one or several hours before the pain begins, the involved joint will begin to tingle, burn slightly, feel warm or just feel different. Sometimes the pain is only mild and merely noticeable for a few hours prior to the severe pain. These warning signs may serve both as diagnostic and as therapeutic aids.

A tophus is a pathognomonic sign of gout. Tophi are found in possibly 2 per cent of patients having their initial attack, but they occur in about 40 to 50 per cent of all cases of gout. An ulceration or draining sinus about a joint suggests gout. Whenever there is doubt that an accessible lesion is a tophus, some of the contents of the tophus obtained by either

needling or scraping the lesion should be examined for the needle-like crystals of sodium urate.

Helpful diagnostic laboratory studies include determination of the blood uric acid level and roentgenography of the involved joint. In initial or early acute attacks the uric acid level may be normal or elevated. All patients with gout should eventually have an elevated blood uric acid level. Some[9] have wondered if those patients with clinical evidence of gout who have a borderline or lower than normal uric acid level do not have an elevated bound uric acid fraction. The blood level of uric acid may be lowered by aspirin in large doses, BENEMID®, ACTH, cortisone, BUTAZOLIDIN® and probably compound F. This uricosuric effect is a variable factor. In the later stages of gout the hyperuremia will be persistent, and with this there may be evidence of renal damage.

The roentgenogram of an involved gouty joint is typical and diagnostic, although early cases of gout may show no abnormalities. The typical picture is one of punched-out areas, usually 5 mm. or more in diameter, located in the subchondral bone of the base or head of the phalanges of the feet or hands. It must be realized, however, that small punched-out areas in bone may also be seen in rheumatoid arthritis and osteoarthritis.

Treatment

The treatment of gout may be conveniently divided into treatment of the acute attack and management of the patient between attacks. As soon as there is any indication of an acute attack of gout, administration of colchicine should be begun, for delay may impair the effectiveness of treatment. If a patient starts taking colchicine as soon as a warning sign is noted, the chances of abating an attack are better than if he waits until severe pain occurs. For this reason it is wise that patients with gout have colchicine available at all times. The dosage is 1/100 gr. every 2 hours day and night until there is relief of pain, or until nausea, vomiting or diarrhea occurs. Then administration of the drug is discontinued. Paregoric may be necessary following the course of colchicine. Usually the tolerance or therapeutic dose of colchicine is between 8 and 14 tablets. After this dosage level has been established, reduction by 1 or possibly 2 tablets may help prevent the severe gastrointestinal symptoms without any loss of effectiveness.

Occasionally, patients may attempt to take colchicine in larger doses or at closer intervals in order to obtain quicker relief, but this will only cause more rapid development of toxicity with less therapeutic benefit. Incidentally, colchicine is so effective in treating acute attacks of gout that it should be used more often as a diagnostic test. A second course of colchicine is necessary in a few cases. Two or 3 days should elapse between courses.

ACTH and cortisone in adequate doses may alleviate most acute attacks of gout, but these seem to have no advantage over colchicine, which is more specific and probably more effective. Moreover, they are not diagnostic, and ACTH withdrawal may precipitate an acute attack of gout in the patient with interval gout unless it is given in conjunction with colchicine.

ACTH has been of value in some cases that are resistant to colchicine. The exact dosage of ACTH has not been established, but it appears that about 60 to 150 mg. in 24 hours may be sufficient to relieve an acute attack. This may be given as a long-acting preparation or in divided doses of lyophilized ACTH. Much less is required if it is administered intravenously over a period of 8 hours. Usually, treatment with ACTH for 24 to 48 hours will relieve acute attacks, after which it can be discontinued, but colchicine should be given from the onset in dosage of 1/100 gr. 4 times daily until gastrointestinal symptoms develop. Then administration of the drug should be discontinued until these toxic symptoms subside (about 24 hours). One or 2 colchicine tablets (1/100 gr.) should then be given daily for at least 2 weeks. Injection of compound F into the gouty joint may also afford relief.[9] In 2 of our patients with gout, colchicine proved effective after this failed to relieve the patient.

Phenylbutazone (Butazolidin) is a new drug recently introduced for the treatment of acute attacks of gout. In divided oral doses of 600 to 800 mg. daily it has proved effective in relieving the symptoms in many patients with acute gout in less than 48 hours. When given parenterally the drug may produce relief within a few hours. If experience with the drug continues to prove successful and the toxicity is not severe enough to be disadvantageous, this drug will be most helpful in treating acute attacks of gout.

In addition to these medications, treatment of the acute attack of gout includes bed rest, large fluid intake and sedation if necessary. The patient usually does not need to be instructed to protect the involved joint. Local hot or cold applications are of little benefit and in some cases may increase the discomfort, but if such applications prove comforting they should be employed. The diet should be such that it does not aggravate a gastrointestinal tract that is handling an irritating agent. A narcotic similar to morphine or codeine may be required to provide comfort before the colchicine becomes effective. Premature resumption of physical activity tends to precipitate additional attacks and for this reason should be carefully avoided.

Management of the patient between acute attacks is important but must be approached realistically. If an asymptomatic patient is seen one or more years after a single brief attack of gout, it would be unreasonable to advise him to follow a strict interval regimen. However, patients having one or more attacks a year should be closely followed and an active interval regimen established.

The diet recommended for patients with gout remains unsettled, and although it appears that the exogenous supply of purines plays a minor role in the pathogenesis of gout, it seems unwise to include such foods as sweetbreads, kidneys and liver in the diet. An adequate diet should be provided but obesity should be avoided.

An adequate fluid intake should be continuously maintained. The alcoholic intake should depend on temperance rather than abstinence. Obviously, any food or fluid which the patient thinks seems to provoke an acute attack should be avoided.

Colchicine tablets (1/100 gr.) may be of value in treating the patient with gout between attacks. One, 2 or even 3 tablets may be given daily in an attempt to prevent rapidly recurring acute attacks. Alteration of the dosage depends on the frequency of the attacks. The drug can be given 3 or 4 days out of each week if daily dosage is not desired. Tolerance to the drug does not develop. If an acute attack occurs during the interval treatment, a full course of colchicine should be given.

Salicylates may be given in daily doses as an analgesic for the painful joints of gouty arthritis. In large doses it also has a uricosuric effect. Daily doses of 50 gr. or more are necessary to enhance uric acid excretion, and when renal calculi or uric acid sand poses a problem, salicylates may be very helpful.

Phenylbutazone in daily doses of 100 to 600 mg. may be helpful in overcoming the symptoms of chronic gouty arthritis. It also has a tendency to lower the serum uric acid level. This, though, requires prolonged use, and toxicity to the drug must be given serious consideration.

A newer uricosuric agent, benemid, which also blocks the tubular reabsorption of uric acid, may be helpful in lowering the uric acid blood level, but it is much too soon to know whether it will be of prophylactic value in recurring acute gouty arthritis. It is not beneficial in the acute attack of gout.

Alkalinization of the urine is recommended in treating the renal complications of gout, for urate is more soluble in an alkaline urine than in an acid urine. This will enhance the increased excretion of urates.

Troublesome tophi can in some cases be removed surgically with excellent results. Patients with chronic gouty arthritis derive temporary benefit from physical therapy but this is not encouraging.

Patients with gout who are to undergo a surgical procedure should be given colchicine (1/100 gr. 2 or 3 times daily) for 2 days before operation and if possible for 2 to 4 days postoperatively.

Summary

Gout is a seldom-remembered but commonly encountered disease in middle-aged men. If recognized early and treated properly, relief of pain can be obtained and articular and renal damage may be prevented. The disease presents a typical pattern which is easily recognized if one is familiar with the clinical picture and keeps the condition in mind. Therapy consists of treatment of the acute attack and management of the patient between attacks. Colchicine is the most effective drug for the great majority of the acute attacks and of value prophylactically in management between attacks. It can also be used as a diagnostic aid. ACTH, cortisone, compound F, phenylbutazone and benemid are newer agents that may also be of therapeutic value.

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Cystic Disease of the Kidneys

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The fundamental pathology of polycystic disease of the kidney, a relatively rare but clinically important congenital malformation, is untreatable. If the pathologic physiology is understood, and a therapeutic regimen is established early through the full cooperation of an internist and a urologist, the lives of patients afflicted with this disease can be prolonged and made more comfortable.

ROBERT BIRCHALL

MARVIN HARVARD

At necropsy many adult kidneys contain one or more macroscopic cysts. These can be classified as follows:

I. Solitary cysts
   1. Simple serous cysts
   2. Dermoid cysts
   3. Endometrial cysts
   4. Parapelvic lymphatic cysts
   5. Peripelvic cysts (pyelogenic)
   6. Echinococcic

II. Polycystic disease
   1. Congenital
      (a) Infantile type
      (b) Adult type
   2. Acquired (retention cysts of contracted kidneys)

Each type of cyst is of potential clinical significance. However, since it is primarily the patient with congenital polycystic disease who constitutes a therapeutic problem for the physician, this discussion will be limited to that entity.

Polycystic disease of the kidneys is a relatively rare congenital malformation characterized anatomically by an excessive number of small and large cysts distributed throughout the parenchyma of the kidney and projecting into its surface. In contradistinction to solitary cysts, which tend to be unilateral and localized most often to the lower pole of the kidney,[1] polycystic disease is probably always bilateral.[2] The often great disparity in the size and degree of involvement of the two kidneys, and the observation that it may not be until years after removal of the polycystic kidney that its mate becomes clinically enlarged, presumably account for the reported incidence of 8 per cent of polycystic kidneys being unilateral.[2,3]

Polycystic kidneys may be conveniently separated into the infantile and adult types. The infantile type becomes apparent shortly after birth and frequently accompanies other developmental anomalies, such as spina bifida, clubfoot and encephalocele.[3,4] The adult type rarely produces symptoms before the third or fourth decade of life and is not regularly associated with developmental anomalies other

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than cysts of the liver which are present in about 30 per cent and cysts of the pancreas which are present in 9 per cent of the patients.[3] The two types probably represent gradations in severity, in that those who do not present clinical evidence of polycystic disease at birth are born with far more normal functioning renal tissue than the others. Lambert,[5] however, has suggested a more specific difference in that in the infantile type the cystic nephrons are always separated from their excretory tubules whereas in the adult type all but the glomerular cysts communicate with their excretory tubule. Although little can be offered the patient with the infantile type, early recognition of the adult type is important not only because careful management may prolong and make more comfortable the patient's life, but also because unnecessary and often dangerous surgical procedures can be avoided.

Etiology

The importance of heredity in the development of polycystic renal disease is well documented. The involved gene is apparently dominant and may be transmitted by either sex.[3] The precise embryologic defect has not been identified. Three theories are most commonly advanced:

1. Ribbert's theory that the newly formed collecting tubules, which originate from the primitive ureter, fail to unite with the appropriate convoluted tubules which have originated independently from the metanephric blastoma. This is a simple and therefore attractive theory, but there is little evidence to support it.

2. Kampmeier's theory, which is based on the assumption that fetal cysts normally appear in the first few generations of detached convoluted tubules, and then subsequently atrophy. In polycystic kidneys these fetal cysts have failed to atrophy or become detached, which prevents the subsequent formation of normal collecting tubules. The end result is a functioning glomerulus attached to a blind cystic tubule.

3. Allen's theory that the cysts result from embryologic atresia or failure of canalization at different levels along the primitive nephron. The basic fault would then appear to be defective integration of the inductive influence of Spemanns' "organizers" or specialized sentinel cells.

Pathology

Typically, polycystic kidneys are enlarged but still retain the shape of a normal kidney. The external surface is studded with elevated areas corresponding to the underlying cysts, and the cut surface shows both the cortex and the medulla to be so filled with cysts that no separation between these portions can be seen. Between the cysts is a variable amount of parenchyma which tends to persist longest in the subcapsular area. The cysts themselves are filled with a substance which ranges from thin aqueous fluid to tenacious colloid-like material to fluid that is dark brown or black.[2] It is high in urea, uric acid and creatinine.

Microscopically, there are several features important to an understanding of the pathologic physiology of polycystic disease:

1. The cysts themselves are apparently of three distinct types.[3,5]

a. Those in whose walls are located normal glomeruli supplied with a patent afferent and efferent arteriole. These are, in effect, dilated capsular spaces[3] and are more frequent in the infantile type of polycystic kidney.[5]

b. Those in which no glomerulus is seen in the wall, and which represent dilated segments of tubules that rarely communicate with the pelvis itself.[3]

c. Excretory cysts which are formed purely from collecting tubules.

2. The cyst wall itself is of flat cuboidal epithelium, which is presumably nonsecretory.

3. Within the cyst wall will often be found the interlobar and interlobular arteries, and in almost every one of the larger cysts numerous arteries lie directly beneath the lining epithelium. As the cysts gradually enlarge, some of the arteries are unable to stretch sufficiently and so describe an arcuate course projecting, with their lining epithelium, directly into the cyst. This explains the common occurrence of hemorrhage into the cyst.[6]

4. In the surrounding parenchyma there is

a paucity of glomeruli,[7] many of which are hyalinized.[2] Directly adjacent to the cyst is a zone of atrophy which suggests that expansion of the cysts progressively decreases the effective functioning parenchyma.[3] In addition, there is an increase in dense connective tissue[6] and considerable thickening of the arterial and arteriolar walls.

Pathologic Physiology

In summary, then, the renal structure is to a greater or lesser degree replaced by innumerable cysts which connect with a glomerulus either directly (subcapsular cyst) or indirectly through a portion of a tubule. Only rarely do they connect with the renal pelvis. Thus, the fluid within the cysts derives wholly from glomerular filtrate, or is a mixture of glomerular filtrate, secretion of the cyst wall, and hemorrhage from the wall into the cysts. Attempts to prove that the cysts actually function to some extent as a nephron[5] have not been conclusive. Renal function, therefore, depends on the number and integrity of the nephrons in the irregularly spaced normal parenchyma. In the infantile polycystic kidney these are too few to support life. In the adult type they are sufficient to maintain it for a variable length of time but slowly, owing to failure of compensatory hypertrophy, increase in the zone of atrophy as the cysts expand, elaboration of a dense connective tissue, and gradual development of arteriosclerosis, renal function diminishes and renal insufficiency appears.

Clinical Picture

If the salient features of the pathology and pathologic physiology of polycystic kidneys are kept in mind, the clinical features presented by the patient who harbors polycystic kidneys become obvious:

1. *Palpable enlargement of one or both kidneys,* which is often unilateral early in the course of the disease, and is rarely detected before the onset of symptoms.

2. *A dull dragging ache in the loin,* which is due to the excess weight of the enlarged cystic kidney, coupled with tension on the renal pedicle.[8]

3. *Episodes of more localized abdominal pain,* with or without fever and leukocytosis. These may be due to infection within the cyst, to distention of the cyst from hemorrhage, or to rupture of a distended cyst into the perinephric area.

4. *Episodes of gross hematuria,* which indicate hemorrhage into a cyst with secondary rupture into the pelvis. Therefore, the hematuria is usually unilateral and is often complicated by renal colic due to passage of blood clots. It is present at some time in 30 to 40 per cent of patients.[8,9]

5. *Episodes of chills, fever and increase in backache* with or without urgency and dysuria. Pyelonephritis occurs in approximately 50 per cent of patients and is severe in 30 per cent.[9] As a secondary phenomenon, about 20 per cent of patients exhibit renal calculi.[4] Dysuria and urgency due to secondary cystitis and urethritis are consequently frequent symptoms of polycystic disease of the kidneys.[10]

6. *Hypertension,* which is present in approximately 60 per cent of patients with polycystic kidneys. This adds to the clinical picture its potential concomitants of left ventricular failure, coronary insufficiency and coronary occlusion, cerebrovascular accidents, and varying degrees of retinopathy which occasionally progresses to papilledema and the malignant syndrome.

7. *Renal insufficiency,* which in the absence of hypertension is usually of slow progression and for years may be virtually asymptomatic. Proteinuria is mild and in the absence of heart failure, edema—although it has been reported—must be considered rare indeed. Ultimately the pallor, weakness, vomiting, acidosis and coma of advanced renal insufficiency appear if death does not first intervene.

Diagnosis and Differential Diagnosis

Considerable bilateral enlargement of the kidneys is almost pathognomonic. When but one kidney is palpable, it must be differentiated from carcinoma of the kidney, hydronephrosis and pyonephrosis. If the correct diagnosis is not clear from the natural history of the disease, including careful inter-

rogation about other members of the family, excretory and retrograde pyelography is most helpful. Typically, these studies reveal elongation of the pelvis with stretching, rounding and widening of the calyces. This may be most diagnostic on the side of the apparently normal kidney. Rarely will exploration be required, but it must be remembered that carcinoma and tuberculosis may be found in the polycystic kidney as well as in the otherwise normal kidney. It is in such cases that renal angiography may be of great help, not only in early diagnosis of polycystic disease but also in detecting coexisting lesions.

Prognosis and Natural Course of the Disease

The average age of onset of symptoms is about 40 years,[4] with the average age of death being 50 years.[2,4] It has been estimated that 45 per cent of patients live less than 4 years after the onset of symptoms,[2,3] 25 per cent live more than 10 years,[3] and 9 per cent live more than 20 years.[3] The average life expectancy, therefore, is somewhat better than 50 years, and the average patient will probably live 10 years after the onset of symptoms and 2 years after the onset of azotemia.[10] If the patient reaches the fifth decade of life without the development of renal insufficiency, he will probably enjoy a normal life span.[2] Statistics such as these are often quoted and may be of some general value, but can scarcely be applied with any assurance to the individual patient. For prognostic purposes it is far better to chart the rate of progression of the disease by evaluating the renal function, cardiac status, blood pressure and appearance of the fundus oculi at regular intervals. Barring an overwhelming complication, it is the rate of progression of the disease which determines the duration of life.

Treatment

Treatment of polycystic renal disease can be conveniently separated into medical and surgical phases. Although it is clear that one should supplement the other, the dividing line between the two has been the subject of much debate, and the exact indications for surgical intervention remain unclassified. Present evidence seems to favor a conservative approach in which medical management forms a constant base line to be altered only by specific indications for surgical intervention.

Medical management—This must vary to a certain extent with the stage of the disease and with the presence of complications. Its primary concern is both comfort of the patient and prolongation of his life. Comfort refers to control of pain in the early stages, and to correction of anemia, fostering of morale, and maintenance of electrolyte and fluid balance when renal insufficiency appears. Prolongation of life refers to the judicious use of a low protein (0.5 gm. per kilogram of body weight), high salt diet for what value it has in decreasing "the work of the kidney" when renal insufficiency appears, and to combating the ever-present threat of infection. Vigorous treatment of associated pyelonephritis is mandatory. Formulation of an adequate therapeutic regimen must take into consideration the results of urinary culture, sensitivity studies against all available antibiotics, and a knowledge of the usual spectrums of each antibiotic.[11] Since an infected cyst has no drainage conduit, and since by their very size the cysts impair the drainage of abscesses in the interstitial tissue that could drain through otherwise normal nephrons, the problem of eradicating infection is rarely more difficult.

Surgical management—If this course of medical management is followed, there may and often will arise certain specific indications for surgical intervention:

1. *Severe protracted abdominal pain.* This is most often caused by distention of large cysts, sudden hemorrhage into a cyst, or displacement of the kidney with traction on the renal pedicle. For relief of pain the involved kidney should be exposed and as many small cysts as possible punctured. Larger cysts may be either excised or enucleated, depending on their location.

2. *Calculus* that is producing obstruction and cannot otherwise be removed. Each must be dealt with as an individual problem, and may require anything from simple lithotomy to nephrectomy.

3. *Persistent infection.* The infection may be confined to a cyst or following rupture of a cyst may involve the perinephric area. If small and localized, an abscess may respond to simple drainage combined with antibiotic therapy. Not infrequently, nephrectomy will be required despite its obvious dangers.

4. *Persistent hematuria.* In most patients this can be controlled by bed rest and repeated transfusions of whole blood. If these fail, exposure of the kidney is necessary. Simple puncture of the cysts may suffice to control the bleeding, but many times nephrectomy is the ultimate requirement. This is, as always, a last resort, since to remove even the smallest amount of functioning renal tissue is to shorten the expected life span of the patient.

5. *Suspected neoplasm.* Occasionally in patients whose disease is predominantly unilateral the pyelogram may suggest a neoplasm. Surgical exploration is then required, but if the kidney is obviously polycystic it is best simply to puncture the cysts and not remove the kidney. It must be remembered, however, that neoplasms do occur in polycystic kidneys and each must be judged individually.

6. *Plastic procedures* on the pelves or ureters of polycystic kidneys are foredoomed to failure. Hydronephrotic kidneys are best removed, provided the remaining kidney can support life.

One of the causes of the progressive impairment of renal function is compression, and subsequent atrophy of normal renal tissue is a direct result of the pressure an enlarging cyst exerts on the functioning parenchyma. In order to minimize this many surgeons enthusiastically advocate exposure of the kidneys and rupture of the cysts either with or without the instillation of sclerosing solutions into the cystic cavities.[12-16] More recently this has been combined with marsupialization and nephropexy. In this operation the kidneys are brought to the skin and suspended there. After healing takes place it is possible repeatedly to aspirate the cysts directly through the scar. Proponents of these methods offer improvement in the pyelograms, reduction in the blood urea nitrogen, improvement in the blood count and a generally improved sense of well-being to support their contention. The benefits last from a few months to several years.

Although enthusiasm is great, the factors that motivate strongly against this radical approach are the fact that the major pathologic defect is that of innumerable small cysts which could not be evacuated by any approach, the necessary destruction of a certain amount of functioning tissue inherent in the procedures, and the dangers of hemorrhage and infection, both or either of which may necessitate a subsequent and otherwise needless nephrectomy. Hope has been expressed that the newer antibiotics would eliminate or at least control the hazard of infection, but this appears to be unlikely. If infection should occur, it will be in a relatively avascular region not amenable to adequate drainage, and therefore not ordinarily responsive to any antibiotic therapy. Thus, at the present time the conservative approach seems justifiable with surgical intervention indicated only for relief of what is tantamount to an immediate surgical emergency.

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Venesection in the Treatment of Congestive Heart Failure, Erythremia, Aortic Aneurysm and Hemochromatosis

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This article presents a reminder of the fact that removing blood from patients is an important therapeutic adjunct in a restricted group of diseases. In some instances venesection may represent definitive therapy of great and lasting value.

THIS paper is not a plea for a return to the bloodletting era of Benjamin Rush, but the physician of today so frequently injects blood into the veins that he is inclined to forget that occasionally it is equally beneficial to withdraw it. Judiciously applied, venesection has a rational place in the management of at least 4 conditions: congestive heart failure, erythremia (polycythemia vera), aortic aneurysm and hemochromatosis.

Congestive Heart Failure

Not much comment need be made concerning the effectiveness of phlebotomy in the management of acute left ventricular failure, for it is obvious that no other measure can so quickly diminish the flow of blood into the right ventricle and thereby reduce its output to a level more nearly commensurate with that which the ailing left ventricle is able to handle. Even in the more chronically ill patient with low cardiac output, high venous pressure and peripheral edema, satisfactory diuresis may not occur until venesection has been done at least once or twice; Howarth and McMichael[1] showed that the effects of venesection or application of tourniquets to the extremities resemble those of digitalis in that all three procedures reduced blood pressure within the right auricle and increased cardiac output in those patients whose hearts were able to respond at all.

The matter becomes more controversial, however, when applied to patients who have congestive phenomena despite a cardiac output which is greater than normal. In general, this situation arises when some peripheral condition increases the need for blood beyond the capacity of even an essentially normal heart to meet the demand (e.g., thyrotoxicosis, anemia, arteriovenous shunt, pulmonary fibrosis). Some[2] believe that under such circumstances a high venous pressure is a compensatory device because it increases cardiac output and that therefore any appreciable reduction in the cardiac filling pressure, such as follows digitalization or venesection, might seriously impair the perfusion of peripheral tissue. Most American clinicians,[3] however, agree that even patients with chronic cor pulmonale and failure of the right ventricle are benefited by measures which reduce venous pressure and blood volume. Although there is a widespread impression that polycythemia is also a compensatory response in patients with chronic pulmonary insufficiency, it is much more likely that its appearance in obstructive emphysema, for example, is an indication of

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heart failure.[4] We have repeatedly observed, following venesection, substantial increases in the maximal breathing capacity of patients with emphysema and secondary polycythemia. The same considerations apply to patients with polycythemia due to congenital heart disease but venesection should be employed cautiously, as abrupt reductions in blood volume are apt to be attended by serious cardiac arrhythmias.

Erythremia

Disorders characterized by an increase in the total mass of the erythron, i.e., total red cell mass, have long been treated by venesection.[5] This definition excludes those conditions in which only the concentration of erythrocytes is increased, such as dehydration or shock; here further reduction of blood volume by venesection is obviously contraindicated.

The cause of erythremia is unknown. There is no significant pulmonary lesion, and arterial oxygen saturation is normal both at rest and after exercise. Arteriolar disease in the bone marrow has not been generally found. The concept that this disorder is neoplastic, a counterpart in the erythroid areas of the leukemias in the leukocytic series, is not in keeping with the clinical course, often measured in decades. Furthermore, the severity of symptoms does not parallel the size of the erythron; whereas, in general, the symptoms worsen as the erythrocyte count increases, the relationship is not constant and linear. The thrombotic tendency, for example, may be greater as the red blood cell count and blood viscosity increase; yet thrombosis not infrequently occurs when the blood count is at or near the normal range.

Although the cause of erythron expansion is not known, irradiation, especially by means of radioactive isotopes of phosphorus, has become the treatment of choice,[6] since it interferes with erythropoiesis, reduces blood volume and controls many secondary manifestations of the disease. Phlebotomy is an effective but less rational alternative for reducing blood volume and total circulating erythrocyte mass. Table 1 illustrates roughly the different responses to bleeding and to P^{32}. Both procedures, if vigorously enough employed, will, of course, result in anemia and hypovolemia, but hemorrhage only serves to stimulate bone marrow activity whereas irradiation depresses it, and bleeding makes great demands on the reservoirs of iron and protein. A reference will also be made later to the effect of venesection on the clotting tendency of blood, a feature not shared by P^{32} therapy. These differences show that venesection should be employed only for quick relief of symptoms or during the latent period required before radioactive materials can exert their full inhibitory effects on bone marrow elements.

When venesection is employed, one must take into account the large basal increase in total blood volume. The first change produced by bleeding is reduction of both plasma and red blood cell volumes, and the physician may be disappointed by the apparent failure of the red blood cell count to decrease following removal of 1 or 2 pints of blood. Removal of several liters of blood over a period of days or weeks may be necessary before the red blood cell and plasma values return to normal.

Great symptomatic improvement may be anticipated from phlebotomy, particularly in the earlier stages of the disease. It will usually be necessary to remove blood periodically in order to maintain the improvement, but the frequency with which venesection is necessary varies greatly from patient to patient,

TABLE 1

BLEEDING VERSUS P^{32}

EFFECT ON	BLEEDING	P^{32}
Blood volume	↓	↓
Hematocrit	↓	↓
Leukocyte	↑	↓
Platelets	↑	↓
Clotting tendency	↑	↓
Iron utilization	↑	—
Protein utilization	↑	—

often from 500 ml. every few weeks to one such venesection in many months once normal levels have been reached.

Aortic Aneurysm

Unquestionably, the incidence of aortic aneurysm is far less today than it was before syphilis became a relatively trivial disease, but treatment has advanced little in the past 100 years. Of the various surgical measures which have been devised, none is uniformly effective.

Venesection for aortic aneurysm was commonly employed in the seventeenth and eighteenth centuries. Osler's[7] account of it is as follows: "To promote coagulation in the sac certain methods are followed which, by increasing the coagulability of the blood and slowing the circulation in the sac, favour the natural processes of cure. The oldest is that of Valsalva, reported by Morgagni: 'The essence of this treatment was to detain the patient very strictly in bed for 40 days, and during this period to subject him to repeated bleedings, while at the same time the diet and drink were carefully ordered, so that the daily allowance, administered in three or four meals, should never be such as to fill up the blood-vessels.' 'He made it a custom,' says Morgagni, 'to diminish the quantity of meat and drink more and more every day, till it was brought down to half a pound of pudding in the morning, and in the evening half that quantity, and nothing else except water, and this also within a certain weight. After he had sufficiently reduced the patient by this method, so that, by reason of weakness, he could scarcely raise his hand from the bed in which he lay, the quantity of aliment was increased again by degrees till the necessary strength returned so as to allow of rising up.'

"It is suggested that the pulsation in the aneurysm can be arrested entirely by this method; but even should the arrest be not quite complete at first, the disease may still be in course of cure if the patient will continue to submit to a modified and strict, but not quite so severe, regimen for some time to come. The difficulty in carrying out this treatment effectively, as stated by Morgagni (no doubt on the basis of Valsalva's experience, as well as his own), is that 'there will be many to whom this method of cure may seem much more insufferable than the disease itself; especially as the only time when it can be of use (the beginnings of the aneurysm) is when the inconveniences actually felt are slight, so that patients are easily led to delay until continuous and grievous suffering, or even impending death itself, can no longer be avoided by any remedy whatever.' The discussion that follows is very interesting, and may perhaps admit of the inference that failures of Valsalva's method were already well known in Morgagni's time, but were attributed (as failures usually are) to the remedy not having been adopted in time. But another inference follows even more clearly from this long discussion by the great pathologist of the eighteenth century, and from the cases submitted in illustration—namely, that with all his respect, amounting almost to veneration, for Valsalva, Morgagni seems to have used the method very tentatively, and with no inconsiderable misgivings (Gairdner). A modification of this was introduced by Bellingham and Tuffnell, and is known by the name of the latter surgeon, the omission of blood-letting being the only point of difference from Valsalva's method."

Recent treatises have scarcely mentioned the procedure, however, even as a curious relic, but Marzullo's[8] spectacular case published in 1940 prompted us to test its efficacy. His patient was a 57 year old Italian man with a forcefully pulsating lobular mass, 9 cm. in diameter and 6 cm. deep, below the suprasternal notch. There were no distressing symptoms, syphilis was denied and serologic tests for syphilis yielded negative results. Fluoroscopy and roentgenography revealed a large aneurysm of the ascending portion of the aorta projecting through the sternum. At

FIGURE 1A. Aort aneurysm protru ing through th sternum.

FIGURE 1B. Fou months after trea ment by phlebotom (courtesy of Mar zullo[8]).

FIGURE 2 rysm of before th

FIGURE 3 cified an dominal congest placemen anteriorly

weekly intervals 3500 ml. of blood were removed in 2 months, at which time the aneurysm was demonstrably smaller. Phenylhydrazine in varying dosages was given for an additional period of 7 months. Figure 1B shows the result after 4 months' treatment. When last seen the gentleman was leading a comfortable, vigorous life at the age of 71 years with little to show for his experience except a large hole in the sternum.

We have treated 10 patients with aortic aneurysms by repeated venesections. One had a calcified abdominal aneurysm; the remainder had aneurysms in the thoracic aorta, one of which was of the dissecting type. All were large enough to cause symptoms. One aneurysm had been "wired" previously but continued to enlarge in spite of the combined treatment. Two other patients treated by phlebotomy alone failed to improve. The remaining 7 were all relieved of pain, and to some extent of other symptoms and signs such as cough, compression of surrounding structures, and dyspnea. The patient with a dissecting aneurysm obtained no relief of pain from large doses of morphine, but after removal of 1500 ml. of blood in a period of 3 days, opiates were not required and within a week the patient had no pain whatever.

The treatment we have employed is to remove 500 ml. of blood daily or every other day until the hemoglobin reaches a level of 6 gm. per hundred milliliters. Unlike Marzullo we have not attempted to maintain the anemic state. When it occurred at all, symptomatic relief was striking. Five of the 7 successfully treated patients have been observed for more than 2 years. Two have been bled a second time because of the recurrence of symptoms approximately 6 months after the first treatment. In no instance was the size of the aneurysmal sac altered, but what might have happened had the anemia been prolonged remains speculative. The spectacular rise in platelet concentration reported by Marzullo was not observed in our cases, but our laboratory data were acquired in a routine manner and more accurate studies of the clotting mechanism are needed. Illustrative of the response of patients with aortic aneurysm to phlebotomy are the following cases.

Case 1—Mr. A. D., aged 55 years, complained of pain in the right side of the chest on exertion for one year. Six months before admission severe pain in the right side of the neck was followed by unconsciousness. Constant pain then developed in both upper extremities, both shoulder regions and the back of the neck. Both hands became swollen and the veins of the neck and upper extremities were distended. Within 2 weeks contractures appeared in both hands and he was unable to extend the fourth and fifth fingers. He also became dyspneic on slight exertion.

Roentgenograms of the chest, fluoroscopy and angiograms demonstrated a large pulsating aneurysm of the ascending aorta (Figure 2). Syphilis was denied and results of tests for syphilis were negative. The red blood cell count was 4,400,000 per cubic millimeter, hemoglobin 13.5 gm. per hundred milliliters and hematocrit 43 per cent.

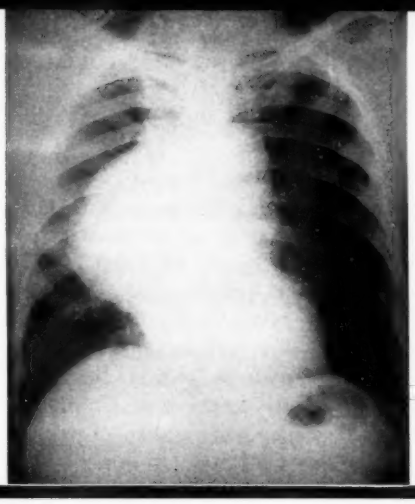

FIGURE 2 *(left)*. Aneurysm of thoracic aorta before therapy.

FIGURE 3 *(right)*. Calcified aneurysm of abdominal aorta causing congestion and displacement of stomach anteriorly to left.

Sixteen hundred milliliters of blood were withdrawn in a period of 4 days. The final erythrocyte count was 3,200,000 per cubic millimeter, hemoglobin 8.4 gm. per hundred milliliters and hematocrit 32 per cent. At the end of one week the patient no longer felt pain and his exercise tolerance had improved. Venous distention had appreciably diminished and motion of the hands had improved. The size of the aneurysm remained unaltered but fluoroscopy indicated less forceful pulsations. At home modified bed rest and a low protein diet were continued for 3 months. At this writing, a year later, the patient is active in his business and has no symptoms. The size of the aneurysm remains the same, but pulsations are minimal. Contracture of the fourth and fifth fingers persists.

Case 2—For 3 years Mr. C. S., aged 50 years, had had pain in the epigastric and left costovertebral areas, which had become constant for the past year. He had been conscious of a hard mass in the abdomen for about 4 years. For 2 weeks prior to admission he had had difficulty in swallowing solid food.

Examination revealed a large pulsating mass filling the midepigastrium. Tests for syphilis yielded negative results. A large calcified mass measuring 13 cm. in diameter was demonstrated roentgenographically in the epigastrium at the level of the twelfth thoracic and first and second lumbar vertebras. Roentgenograms of the upper gastrointestinal tract showed compression of the lower portion of the esophagus by the aneurysm with dilatation above (Figure 3). The stomach was displaced forward and to the left. The red blood cell count was 4,800,000 per cubic millimeter, and hemoglobin 14.6 gm. per hundred milliliters.

A total of 3000 ml. of blood was removed in amounts of 500 ml. over a period of 9 days. After the third phlebotomy, dysphagia disappeared, and the patient no longer complained of pain. The final hemoglobin reading was 6.3 gm. per hundred milliliters. At home the patient continued the treatment of bed rest and a low protein diet for 3 months, after which he returned to work.

One year later the patient was readmitted. Nine months after his first hospitalization, left costovertebral pain appeared and became progressively worse. Dysphagia had been present for 2 months before readmission. He had also noted a "pulling pain in the throat" for 2 months. Results of physical examination were unchanged. The roentgenographic findings differed only in that on this admission bony erosion of the anterior margins of the bodies of the first and second lumbar vertebrae was noted. The red blood cell count was 4,200,000 per cubic millimeter and hemoglobin 11.9 gm. per hundred milliliters.

Twenty-five hundred milliliters of blood were withdrawn in amounts of 500 ml. over a period of 7 days. The final red blood cell count was 2,800,000 per cubic millimeter and the hemoglobin 8.4 gm. per hundred milliliters. Dysphagia disappeared after removal of 1000 cc. of blood, and at the time of discharge 10 days after admission he no longer complained of pain. The patient is again

working, 9 months after the last admission, and complains only of intermittent "aching in the back."

It is not implied that phlebotomy is an ideal or even a rational treatment for symptomatic aortic aneurysms. However, in 70 per cent of the cases in our limited series it was followed by a degree of symptomatic relief which we have not seen before. We are in no position even to speculate about the mechanism of relief from pain and pressure, though one naturally wonders about the effect of bleeding on fibrin deposits.

Hemochromatosis

Hemochromatosis is another disorder which responds remarkably to phlebotomy.[9,10] It is a disease characterized by hepatic cirrhosis, diabetes mellitus, bronzing of the skin and widespread deposition of iron pigment with special concentration in the liver and pancreas. The total amount of iron in the body may be increased fortyfold.

Phlebotomy as rational therapy in this condition receives support from recent studies which define the metabolism of iron in normal persons and in those with hemochromatosis.[11-14] In hemochromatosis the normal intestinal barrier to absorption of iron seems to be at least partially defective so that the absorption continues regardless of saturation of the body stores. Since no mechanism for excretion of iron exists (except hemorrhage), the excess element is deposited as hemosiderin, and it is apparently this pigment which induces fibrosis, particularly in the liver and pancreas. Convincing proof is now available that the iron in hemosiderin is available for hemoglobin synthesis.

Since 1 liter of blood contains only approximately 0.5 gm. of iron and since in hemochromatosis the liver alone may contain as much as 60 gm. of iron pigment, enormous amounts of blood must be removed to reduce the iron content of these storage depots materially. Our procedure, therefore, has been to remove blood at the rate of 2 to 4 liters a month and after each bleeding to separate and reinject the blood plasma in order to minimize loss of protein stores. The usual dietary and supportive measures for cirrhosis and for diabetes mellitus are, of course, also employed. No attempt is made to limit the iron content of food, since relatively enormous quantities of iron are being removed by means of phlebotomy.

Five patients have been thus treated with exceedingly encouraging objective and subjective improvement. One patient with advanced disease died of primary carcinoma of the liver about 6 months after institution of the therapeutic regimen. The other 4 have experienced renewed vitality and have been able to resume full activity, which they had been previously forced to abandon. The liver has decreased in size, liver function has returned toward normal, insulin requirement has diminished and in those with cardiac abnormalities electrocardiographic improvement has occurred.

Of particular interest is the extremely rapid rate at which hemoglobin synthesis has occurred in these patients. This is graphically illustrated by one patient who was able to maintain a normal blood count despite removal of 50 liters of blood in 60 weeks.

The following case (reported elsewhere[9] in detail) illustrates a spectacular response to phlebotomy.

Case 3—An osteopath, aged 47 years, complained of such severe fatigue that he was forced to abandon his practice about 10 months previously. He admitted excessive indulgence in alcoholic beverages for the previous 5 years. He had experienced episodes of confusion and disorientation 5 months before admission.

Examination revealed a blood pressure of 144 mm. of mercury systolic and 100 mm. of mercury diastolic in both arms. A bluish discoloration of the skin, particularly about the ankles, was noted. The liver was palpated 8 cm. below the right costal margin but the spleen could not be felt.

Laboratory tests showed the red blood cell count to be 4,900,000 per cubic millimeter, hemoglobin 14.9 gm. per hundred milliliters, hematocrit 41.5 per cent, fasting blood sugar 150 mg. per hundred milliliters (an average of several determinations), prothrombin level

49.6 per cent, serum albumin 3.2 gm., serum globulin 2.6 gm., and BROMSULPHALEIN® retention 4 per cent at 45 minutes. The electrocardiogram revealed low T waves in leads I, II and V_4 to V_6. Liver biopsy disclosed hemochromatosis with extensive deposition of iron pigment throughout the sections as well as moderately advanced cirrhosis.

Thirty-three liters of blood were removed during a period of 35 weeks and the plasma was replaced. During that time the patient noted remarkable increase in energy and resumed full-time practice. When seen 8 months after admission, bromsulphalein retention was 3 per cent in 45 minutes, total serum protein 6.6 gm. (albumin 4.0 gm., globulin 2.6 gm.), prothrombin 100 per cent, fasting blood sugar 123 mg. per hundred milliliters, hemoglobin 13.7 gm. per hundred milliliters and red blood cells 5,000,000 per cubic millimeter. Liver biopsy revealed decrease in the concentration of iron pigment in all areas, but most pronounced in the areas of healthy hepatic parenchyma, and complete disappearance of inflammatory reaction within the hepatic lobules. When seen again 20 months after admission his condition was apparently normal. On deep inspiration, the liver was barely felt 2 cm. below the costal margin. Total serum proteins were 5.5 gm. (4 gm. albumin, 1.5 globulin), bromsulphalein retention 4 per cent, and fasting blood sugar 116 mg. per hundred milliliters. An electrocardiogram showed no abnormalities and liver biopsy revealed no iron pigment and alterations indicative of inactive or healed cirrhosis. One month later he seemed to be perfectly well, but venesection will be repeated as often as is necessary to keep the erythrocyte count at slightly subnormal levels.

Summary

Phlebotomy is a useful therapeutic procedure in the management of the following conditions:

1. Congestive heart failure—It affords the speediest way of reducing venous pressure and of increasing the output of an overloaded left ventricle.

2. Erythremia (polycythemia vera)—It quickly reduces blood volume and relieves symptoms, but radioactive phosphorus is a more rational approach because it depresses erythropoiesis whereas bleeding stimulates it.

3. Aortic aneurysm—Pain and symptoms produced by pressure were quickly relieved by venesection in 7 of 10 patients with aortic aneurysm, thus confirming the value of venesection known to the ancients but recently forgotten. The mechanism of this relief is unknown since the aneurysmal sacs appeared not to diminish in size.

4. Hemochromatosis—Repeated massive venesection with plasma replacement greatly improved 4 of 5 patients because the increased demand for new erythrocytes required utilization of the iron deposits so characteristic of the disease.

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GENERAL PRACTICE *Review*

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Endocrine Therapy in Gynecologic Disorders

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THE therapeutic approach to some of the disturbances seen in gynecology related to dysfunction of the glands of internal secretion may at times be problematic and perplexing. Confusion on this matter leads on the one hand to overenthusiasm and misguided endocrine therapy and on the other to unjustified surgical intervention. The voluminous literature prevalent on the therapeutic approach to problems in gynecology further substantiates the lack of unanimity among the different workers in the field on the proper management of some of the common functional disorders seen in the female. For example, we are cognizant of the fact that excessive uterine bleeding of proved physiologic origin has been overtreated with hormones or the endometrium has been amputated by surgical curettage. Advocates for either procedure base their approach to the problem on inclination rather than on the more propitious form of therapy. A much greater diversity of opinion has been offered in the therapy of primary or intractable dysmenorrhea. Totally different methods of treatment based on equally divergent theories of the pathogenesis of dysmenorrhea have promulgated the use of agents which have been opposite in their action. These agents have varied from the use of extract of raspberry leaves[1] or insulin[2] to the administration of steroid hormones.[3]

On the other hand, extensive claims have been made by the psychiatrically minded that many of the apparent endocrine imbalances seen in the female from the menarche through the menopause are caused primarily by psychosomatic disturbances. Based on such a concept, the psychiatrist suggests that many functional disturbances noted in gynecology can be adequately controlled by a correct psychosomatic approach. Such problems as the loss of libido, the surgical climacteric, and premenstrual molimina have many times been wrongly delegated to the realm of the psychiatrist for treatment by many gynecologists because they believed these aberrations to be due primarily to psychosomatic disturbances and not to any hormonal deficiency as such. However, the judicious use of potent chemical

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substances—hormones—in these selfsame disturbances have produced corrective effects more promptly and physiologically than psychiatric therapy.

The therapeutic management of some of these problems in gynecology will be briefly outlined in this paper. Each subject heading will be considered as a separate entity, and emphasis will be on the physiologic approach to these functional disturbances by adequate hormonal therapy. Additional minor gynecologic procedures can be used in conjunction when necessary, but these will not be elaborated on. The absence of organic changes must be established by a complete gynecologic physical examination. When discovered, they must be removed or altered before one can anticipate a successful response to endocrine therapy. In most conditions in which functional disorders are present, a deficiency or an excess of certain endocrine secretions may be wholly or in part responsible for the disturbed mechanism. The following forms of therapy have proved very effective in the control of some of these perplexing problems.

Progesterone and Testosterone in Control of Functional Menorrhagia

Endocrine control of functional menorrhagia may be very effectively accomplished by the administration of two common steroids—progesterone and testosterone. The use of this combination is based on the particular application of these steroids as follows: Testosterone is employed primarily for its hemostatic effect and not for any specific alteration of the functional disturbance underlying the abnormal uterine bleeding. In the dosage used (25 mg. a day for 5 days) it has been demonstrated that testosterone does not induce any morphologic alteration in the endometrium of these patients.[4] On the other hand, progesterone is utilized for its therapeutic effect in inducing alteration in the endometrial pattern. Progesterone will produce morphologic changes in the endometrium characteristic of the secretory phase. The use of these two therapeutic agents has been a valuable adjunct, based on their twofold action, to the therapy of excessive functional flow.[5,6] The

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addition of estrogen[7] to this combination would not appear to offer any advantage and indeed its use must be considered as superfluous since most cases of excessive uterine bleeding are associated with adequate estrogenic activity as evidenced by the presence of cystic-glandular hyperplasia of the endometrium. It must be emphasized that when testosterone and progesterone are used, oil solutions should be employed rather than aqueous suspensions. The purpose of the oil solutions is to accomplish as rapid a therapeutic effect as possible. Steroid hormones in oil solutions are much more prompt in action, and the active material is made more readily available than is true of similar aqueous suspensions.

Functional uterine bleeding associated with hyperplasia of the endometrium with or without cystic glands is accompanied by incomplete desquamation of the endometrium during the hemorrhagic phase. This is perhaps due to pathologic physiology in that there is no sharp drop in the estrogen level with its concomitant effect on the spiral arteries, so that incomplete intermittent shedding of the proliferative endometrium takes place. This type of desquamation of necessity results in prolonged bleeding. Estrogen must be considered as a growth hormone for the uterus in that it produces growth changes in the endometrium. Progesterone, on the other hand, causes comparatively little growth but induces secretory changes in this tissue when previously primed with estrogens. As a result, following cessation of progesterone therapy, withdrawal bleeding occurs and is followed

by complete desquamation of the endometrium. Desquamation is so complete that this use of progesterone has been referred to as a "medical curettage," a term coined by Fuller Albright some 15 years ago.[8] This is then followed by cessation of uterine bleeding for a period of several weeks.

The control of menorrhagia by this means in patients without underlying organic or neoplastic disease results in essentially the same effect as that obtained by surgical curettage. However, the former type of therapy has the advantage in that, in addition to its immediate therapeutic action, it may lead to definitive changes in the physiologic activity of the individual so that an adjustment may occur and regularity of the menstrual periods may ensue.

Before initiation of therapy it is wise to secure information concerning the nature of the uterine bleeding by obtaining an endometrial biopsy, except perhaps in those adolescent patients just recently past the menarche. Endometrial biopsies obtained before the onset of hormonal therapy and on the first day of withdrawal bleeding will supply irrefutable evidence of the functional nature of the disease (anovulatory in most cases) and substantiate the need for progesterone in inducing secretory changes.

The actual technic of treatment that may be employed follows two lines of application and is dependent on whether oral administration or intramuscular injections are used. The intramuscular method involves the combined administration of 25 mg. of progesterone plus 25 mg. of testosterone propionate per day for 4 to 5 days. This regimen will induce cessation of bleeding during the period of injection, usually on the first or second day of therapy. Withdrawal bleeding produced by normal complete desquamation will occur 3 to 4 days after the last injection, following which the patient will be amenorrheic for a period of 4 to 5 weeks. Without waiting for a spontaneous menstrual period the patient should receive progesterone alone, either as a single 100 mg. dose or in the form of multiple doses of 25 mg. daily for a period of 4 to 5 days, starting exactly 4 weeks after she has received her first combined injection. There is no need for testosterone at this time since the patient is not actively bleeding. Progesterone therapy is repeated at monthly intervals for 2 subsequent months until the patient has been given a total of 4 courses of therapy, the first course consisting of combined testosterone-progesterone therapy and the last 3 courses consisting of monthly administration of progesterone, either as a single injection or as 4 daily injections of 25 mg. each. The purpose of the cyclic progesterone therapy is to decrease the possibility of future recurrence of menorrhagia.

As an alternative to the intramuscular form of therapy, oral tablets have also proved to be effective in the control of menorrhagia, employing essentially the same compounds. Oral therapy has consisted of the use of tablets containing 50 mg. of progesterone and 50 mg. of methyltestosterone. These are administered 4 times a day for a period of 5 days. As a result, the same sequence of events occurs as has been noted following parenteral therapy. The patient will stop bleeding during the period of oral administration. Withdrawal bleeding will occur some 2 to 4 days after the last tablet has been taken. The advantage of this form of therapy, of course, lies in the fact that the patient does not have to present herself for repeated injections. Subsequent to the control of bleeding, progesterone may be given orally in the form of tablets of anhydrohydroxyprogesterone or as a single injection as advocated in the parenteral scheme. The anhydrohydroxyprogesterone should be administered in 10 to 20 mg. doses 3 times a day for 7 days at monthly intervals for 3 months. A diagrammatic presentation of the general scheme of therapy is presented in Figure 1. The characteristic cystic and glandular hyperplastic endometrium recovered at the time of excessive uterine bleeding is noted in Figure 2. The resulting secretory changes observed after excessive uterine bleeding has been controlled by the combined use of testosterone and progesterone are depicted in Figure 3. Such an endometrial pattern is subsequently followed by complete desquamation and withdrawal bleeding.

In passing, precautions to be exercised in using this therapeutic regimen should be em-

phasized. It is important to stress that a "medical curettage" is a procedure that attains its most important application in the treatment of excessive uterine bleeding noted in the young adolescent girl and in women under the age of 30 years. Prior to its use, however, in patients past the age of 30 it is important that early neoplasm as a possible etiologic factor be ruled out at least by cell smear study of both the cervix and the endometrial cavity, and preferably by multiple biopsy and curettage. If there is no evidence of any significant pathologic condition, the combined steroid therapy can then be used and depended on to attain a high degree of successful application without fear of overlooking an early neoplasm. When these precautions are exercised it is believed that this form of therapy can be used with little fear of missing an early carcinoma. Moreover, failure to respond to therapy, in patients of any age group, should be an indication for hysterography which may identify small benign intrauterine lesions such as polyps, submucous myomas or adenomyosis.

The advantages of hormone therapy are as follows:

1. It is a physiologic method of controlling functional uterine bleeding.
2. The procedure is nontraumatic, even to the psyche.
3. As a result of the use of progesterone this combined treatment tends to lead to permanent correction.
4. It is an office procedure or may actually be completed outside of the office by oral therapy.
5. This procedure is economically feasible for all classes of patients. The cost of medication, whether taken orally or intramuscularly, is far below that entailed by surgical curettage.

It is important, however, to note that a diagnostic curettage does have one important advantage, in that pathologic examination of the curettings is possible. Such an examination is impossible when the medical curettage is employed. This fact makes it necessary to keep in mind that excessive uterine bleeding may well have an undetected organic back-

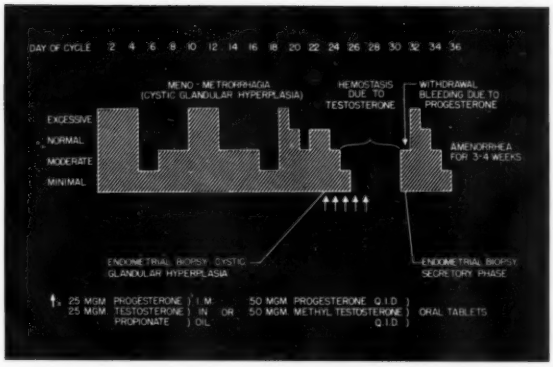

DAY OF CYCLE 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36
MENO - METRORRHAGIA (CYSTIC GLANDULAR HYPERPLASIA)
HEMOSTASIS DUE TO TESTOSTERONE
WITHDRAWAL BLEEDING DUE TO PROGESTERONE
EXCESSIVE
NORMAL
MODERATE
MINIMAL
AMENORRHEA FOR 3-4 WEEKS
ENDOMETRIAL BIOPSY, CYSTIC GLANDULAR HYPERPLASIA
ENDOMETRIAL BIOPSY, SECRETORY PHASE
25 MGM. PROGESTERONE } I.M.
25 MGM. TESTOSTERONE PROPIONATE } IN OIL
OR
50 MGM. PROGESTERONE Q.I.D. }
50 MGM. METHYL TESTOSTERONE Q.I.D. } ORAL TABLETS

FIGURE 1. Graphic presentation detailing response of patient with functional uterine bleeding to combined progesterone-testosterone therapy, resulting in "medical curettage."

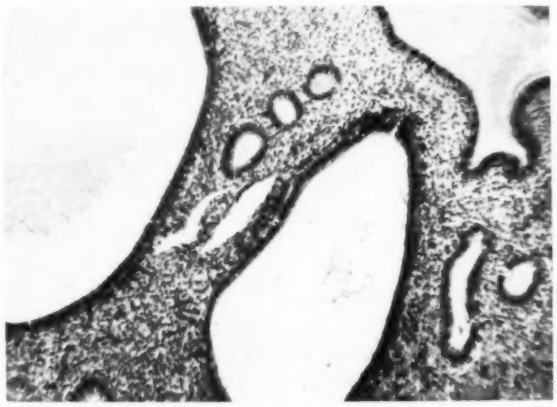


FIGURE 2. Endometrial biopsy obtained during period of functional uterine bleeding prior to testosterone and progesterone therapy, showing typical cystic and glandular hyperplasia of the endometrium.

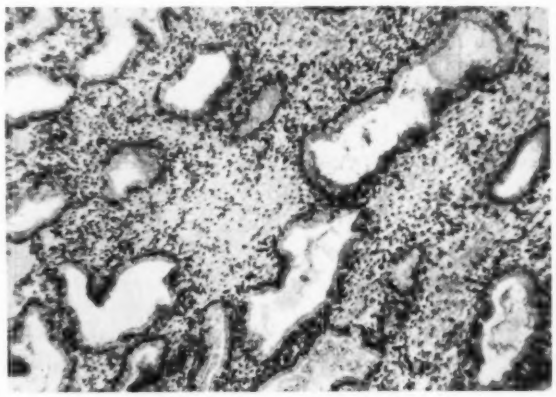


FIGURE 3. Endometrial biopsy obtained after testosterone and progesterone therapy on first day of "medical curettage," showing typical secretory changes.

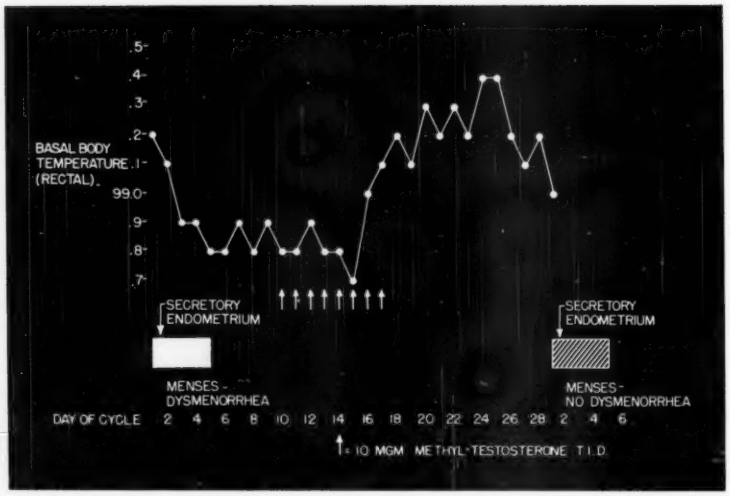
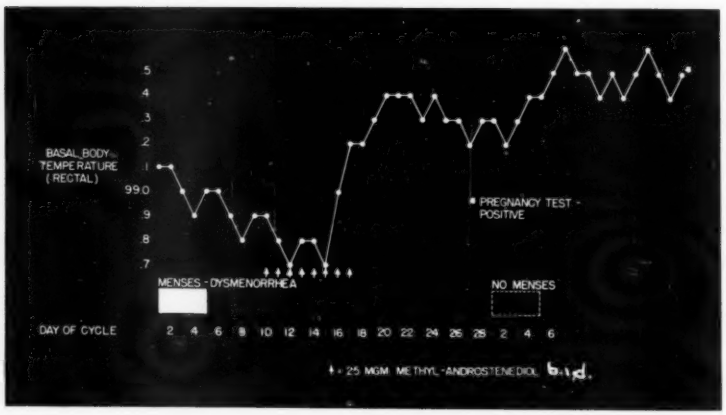

BASAL BODY TEMPERATURE (RECTAL)
99.0
SECRETORY ENDOMETRIUM
MENSES - DYSMENORRHEA
SECRETORY ENDOMETRIUM
MENSES - NO DYSMENORRHEA
DAY OF CYCLE 2 4 6 8 10 12 14 16 18 20 22 24 26 28 2 4 6
+ = 10 MGM METHYL-TESTOSTERONE T.I.D.

FIGURE 4 *(left)*. Basal body temperature graph showing ovulatory rise in temperature following preovulatory administration of methyltestosterone.

FIGURE 5 *(below)*. Basal body temperature chart exhibiting ovulatory rise in temperature following the preovulatory administration of methylandrostenediol. Patient became pregnant during hormone administration.


BASAL BODY TEMPERATURE (RECTAL)
99.0
PREGNANCY TEST - POSITIVE
MENSES - DYSMENORRHEA
NO MENSES
DAY OF CYCLE 2 4 6 8 10 12 14 16 18 20 22 24 26 28 2 4 6
+ = 25 MGM METHYL-ANDROSTENEDIOL b.i.d.

ground. The precautions against the erroneous use of hormone therapy in such cases have been previously emphasized.

Hormonal Control of Functional Dysmenorrhea

Since a complete discussion and review of the literature on the treatment of dysmenorrhea is beyond the scope of this discussion, only endocrine factors in therapy will be outlined. Briefly it may be said that the modern hormonal approach to the therapeutic management of dysmenorrhea has been based on the concept that this symptom occurs primarily only in those women who have a secretory endometrium; i.e., dysmenorrhea, functional in nature, is rarely if ever observed in patients in whom ovulation does not take place. This concept, first promulgated by Wilson and Kurzrok[9,10] and elaborated on by Sturgis and Albright,[11,12] led to a widely accepted form of therapy consisting primarily of the suppression of ovulation by the use of excessive doses of estrogen administered during the first half of the menstrual cycle.[11,12] While painful menstruation is controlled by this procedure in many patients, it must be considered an unphysiologic approach to the problem because it is apt to lead to a disturbance in menstrual rhythm. In an attempt to develop a form of therapy which would not abolish ovulation or disturb the cycle, the regimen to be described has been employed with a fair degree of success. It is dependent on the use of either methyltestosterone or methylandrostenediol.[3,6] The former preparation is administered in 10 mg. doses 3 times

a day for a period of 8 days. The latter drug (a protein anabolic steroid having low androgenic activity) is administered in 25 mg. doses twice a day for the same period of time. Either one of the preparations is started at the same time of the cycle, i.e., on the tenth day of a 28 day cycle. The patient receives these steroid hormones starting approximately 4 days before the expected day of ovulation and continued until approximately 4 days following its occurrence. In the case of a patient with a 30 day cycle therapy would be initiated on the twelfth day, while a patient with a 26 day cycle would receive the androgen on the eighth day of her period. A diagrammatic scheme of the actual timing of therapy with methyltestosterone or methylandrostenediol is shown in Figures 4 and 5, respectively, indicating the proper sequence of events.

The use of either one of these drugs in this fashion has proved an effective form of treatment for many patients with dysmenorrhea. While they control pain, it is important to emphasize that they do not act by inhibiting ovulation nor do they disturb menstrual rhythm. The fact that ovulation is not inhibited is evidenced by 3 types of data:

1. In those patients in whom basal body temperature curves were followed, a rise in temperature curve was noted at the time of ovulation (Figures 4 and 5).

2. Endometrial biopsies obtained in these patients on the first day of menstrual flow showed a secretory endometrium despite the fact that the dysmenorrhea had been controlled (Figure 6).

3. Several patients under this form of treatment have become pregnant (Figure 5).

The advantages of the preovulatory use of methyltestosterone and methylandrostenediol in the treatment of dysmenorrhea are:

1. It is an effective form of therapy in many individuals and has given positive results when other forms of therapy have failed.

2. Ovulation is not inhibited, despite the fact that the drug is started 4 days before the onset of ovulation.

3. The dose is usually not masculinizing, although some patients on methyltestosterone have remarked that while under treatment an enhancement of libido has occurred.

4. There is no decrease in the effectiveness of the preparation on repeated usage.

5. One may reiterate that these preparations may be used with little concern in those cases in which sterility is a problem. In fact it may be an advantage to use these preparations since it has been noted that methyltestosterone has a relaxing effect on tubal spasm, a phenomenon noted in some women at the time of ovulation.[13] Methylandrostenediol may have the added advantage over methyltestosterone in that it will not increase libido in the doses used.[3] In the over-all analysis of our data methyltestosterone has proved to be somewhat superior to methylandrostenediol in controlling pain. Nevertheless, both drugs have proved to be effective in some patients in whom no form of therapy was effective in controlling dysmenorrhea in the past.

It is interesting to note that this regimen has been effective also in controlling premenstrual tension in those patients in whom dysmenorrhea has been associated with menstrual molimina. By the use of a single drug one is able to control two distressing symptoms associated with the menstrual cycle.

The mechanism of action of methyltestosterone and methylandrostenediol in controlling

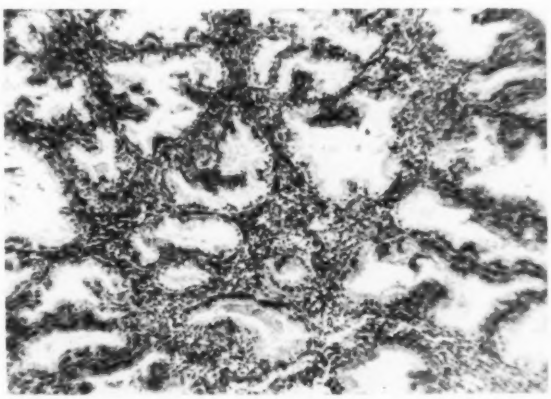


FIGURE 6. Endometrial biopsy obtained on first day of menstruation of a patient who received preovulatory methyltestosterone. The patient did not experience dysmenorrhea despite the characteristic secretory endometrium indicating that ovulation was not inhibited.

dysmenorrhea and/or premenstrual tension is not known but perhaps may be associated with the fact that each has a methylated group at the seventeenth carbon atom. This may be an important factor in suppressing or preventing pain, since the use of a drug in which an ethinyl group is substituted for the methyl group has proved to be ineffective in controlling painful menstruation.[3] Thus it was noted that the preovulatory administration of ethinyltestosterone (anhydrohydroxyprogesterone) was valueless in the treatment of dysmenorrhea. As a matter of fact, if this preparation is given premenstrually, dysmenorrhea may be actually accentuated.

The Climacteric

In either the natural or the surgical climacteric, hormonal therapy has a proved place in controlling symptoms which are of great distress to the patient. While many of the presenting complaints may be considered psychosomatic in origin, it is generally accepted that they occur promptly in most individuals when there is a sudden decrease in the production of estrogens by the ovary. Apparently cessation or diminution of ovarian activity either at the menopause or induced artificially by surgical removal of the ovaries can result in numerous symptoms characterizing the climacteric syndrome. However, despite the appearance of this symptom complex, it is apparent that not all such patients are in need of hormonal replacement therapy. By carefully controlled studies in our clinic, using blind testing procedures whereby neither the physician nor the patient knows what drug she was receiving, we have demonstrated time and time again that a placebo will be effective in approximately one-third of our patients.[14] However, the other two-thirds who are bona fide climacteric patients respond fairly poorly to sedation therapy but do exceedingly well with the proper application of estrogen or estrogen and androgen medication. In this latter group about 10 per cent failures are encountered.[14]

The surgical menopause is usually of greater severity depending on the patient's age at the time of surgery. Due to the severity of symptoms frequently occurring in the younger surgical castrate, more intensive endocrine therapy is necessary to control these patients. The approach to therapy of the surgical menopause may be associated with a high degree of success accompanied by little or no discomfort to the patient if prompt implantation of pellets of the sex steroids is undertaken at the time that surgery is performed.[6,15] This can be done by inserting three 25 mg. pellets of estradiol plus two 75 mg. pellets of testosterone in the rectus muscle on closing the abdomen following bilateral oophorectomy and total hysterectomy. This procedure should

FIGURE 7. Pellet implantation. Small knife stab wound being made after proper antiseptic preparation of skin following local anesthetic. Area of implantation: right inguinal region.

FIGURE 8. Pellet implantation. A trochar being inserted into stab wound.

be restricted to those patients in whom total hysterectomy and bilateral oophorectomy are carried out and is particularly valuable in patients less than 40 years of age. In patients in whom there is a suspicion of malignant disease or of endometriosis, it is wise to defer hormone therapy until a full pathologic report is obtained.

With the use of pellets of estradiol and testosterone, we have been able to control the symptoms of the usually severe climacteric. The purpose of the addition of the testosterone to the estradiol pellets is to give the patient a greater feeling of well-being. In addition, in those patients in whom the factor of libido is of significant consequence, the androgens will usually prevent any loss of libido as a result of the surgical procedure. In adhering to this technic in some 50 to 60 patients, we have observed sloughing of the pellets in only one patient. Here the patient had experienced postoperative hemorrhage in the wound area and the pellets were extruded from the disrupted incision. Pellet implantation is well tolerated, and as long as the total hysterectomy has been accomplished and the ovaries have been completely removed, the possibility of undesirable sequelae is remote. The insistence on the total hysterectomy is based in part on the fact that the pellet implantation with an intact uterus may be followed by uterine bleeding due to the excessive and persistent estrogenic stimulation. None of the patients receiving the estradiol pellets alone or in conjunction with testosterone have complained of breast tenderness or the development of alteration in breast tissue. The duration of action of the pellets has been some 15 to 20 months. Vaginal smears taken from some patients up to 2 years after implantation still show a normal degree of cornification. Only rarely have patients required any additional oral estrogen therapy if they had received 75 mg. of estradiol in pellet form.

The treatment of the natural climacteric revolves around the use primarily of sedation, estrogens and combinations of estrogen and androgen. As discussed previously, we found that one-third of our clinic patients will respond very adequately to placebo therapy.[14] The other two-thirds will show only a fair response to sedation therapy and of necessity require estrogen or estrogen-androgen therapy. No information is available as to the number of women in the menopausal group who have symptoms justifying therapy. It is believed that a large proportion may not need treatment and rapidly adjust themselves.

The majority of the clinic patients requiring therapy will show an adequate therapeutic response to physiologic doses of estrogen or estrogen and androgen. Only rarely did any of the estrogens in the doses used in our study induce any uterine bleeding. However,

FIGURE 9. Pellet implantation. The pellet placed in injector prior to insertion of plunger.

FIGURE 10. Pellet implantation. Completion of procedure with opening closed with single 0000 suture.

none of the estrogens employed appeared to have a selective effect on symptoms with minimal effects on the endometrium. Use of any of the estrogens in adequate and comparable doses induced uterine endometrial stimulation. The combination of estrogen and testosterone results in a synergistic response whereby one can give a lesser dose of either material and still get an increase in the summation of their therapeutic response.[16-18] In other words, masculinizing phenomena following the androgen therapy in the doses employed will be minimal or absent and, in addition, withdrawal bleeding or evidence of hyperestrogenism will likewise be minimal or unlikely. Of the various estrogens used, we have found daily doses of the following preparations to be effective in producing adequate control of the female climacteric:

1. Ethinyl estradiol, 0.05 mg.
2. Conjugated estrogens (equine), 1.25 mg.
3. Dienestrol, 0.5 mg.
4. Tri-p-anisyl chloroethylene, 12.0 mg.
5. Equilin, 0.5 mg.

In combination with androgen, the following preparations and the doses employed proved to be efficient when administered once daily:

1. Conjugated estrogens (equine), 0.625 mg. plus 5.0 mg. methyltestosterone.
2. 1.0 mg. estradiol plus 10.0 mg. methyltestosterone.
3. 0.02 mg. ethinyl estradiol plus 5.0 mg. methyltestosterone.
4. 0.5 mg. stilbestrol plus 5.0 mg. methyltestosterone.
5. 0.25 mg. dienestrol plus 5.0 mg. methyltestosterone.

It has been suggested that the combined therapy of estrogen and androgen is more advantageous in controlling the osteoporosis of the climacteric.[19,20] Testosterone will augment the protein anabolic effect of estrogens. Also, the addition of testosterone will many times enhance libido when estrogen may fail to do this by itself. Androgens in the doses employed may have a greater ameliorating effect than estrogens alone on the anxiety state and increased nervousness noted in many climacteric patients. The duration of therapy, of course, depends on the age of the patient, the severity of symptoms and the response to the original therapeutic dose employed. The younger the patient, especially when the climacteric is surgical, the longer will there be a need for therapy. The older the patient in the natural climacteric, the shorter will be the duration of therapy.

It is important to note that in attempting a reduction of therapy, a gradual decrease must be undertaken over a relatively long period of time. In other words, instead of abruptly terminating therapy, one should reduce the dose in half and maintain the patient on such daily doses for one month. Then reduce the daily dose still further and maintain them on that for another month, following which the therapy should be instituted once every second or third day until all estrogen is discontinued. Under such circumstances the patient will probably have little or no withdrawal symptoms.

The addition of testosterone to the estrogen in oral therapy is for a threefold purpose:[18] (1) to increase the general feeling of well-being and favorably influence the protein anabolic effect of estrogen; (2) to decrease the amount of estrogen that would ordinarily be required to control the menopausal symptoms; (3) it has been found that testosterone will increase libido in those patients who have experienced libido in the past. The question of libido will be discussed further in another section.

Atrophic vaginitis, a complication of the elderly postclimacteric patient, is a specific distressing complaint due to profound and prolonged estrogenic deficiency. These patients can be treated very adequately by the topical application of estrogenic substances in either suppositories or creams. Either form of medication is used once daily for a period of 10 to 14 days, following which therapy is discontinued and reinstituted only if the vaginitis recurs. Suppositories containing 2000 or 5000 I.U. of estrogenic substances have been employed. The creams that have been utilized contained one of the following estrogens in the specified dose per gram of ointment:

1. 0.05 mg. ethinyl estradiol.

2. 1.25 mg. conjugated estrogens (equine).
3. 1.0 mg. stilbestrol.

The advantage of suppository or ointment therapy in atrophic vaginitis is that a localized effect is achieved with little or no systemic response.

It may be necessary at times to implant pellets of estradiol in patients following recovery from surgery consisting of a total hysterectomy and bilateral ovariectomy. In so doing there are a number of excellent instruments on the market whereby a subcutaneous implantation can be undertaken with relatively little discomfort or pain to the patient. This procedure should be carried out in the office and is accomplished by first infiltrating the area of the skin with 1 per cent procaine after proper application of local antiseptics (Figure 7). The same dose of pellets inserted at the time of operation is recommended, i.e., three 25 mg. pellets of estradiol with two 75 mg. pellets of testosterone.

The insertion of the pellets may be either in the subscapular or in the right or left inguinal region. The actual technical insertion of the pellets is easily performed, and the procedure is illustrated in Figures 7 to 10.

Endocrine Allergy

The concept of allergy to the presence of native hormonal substances is receiving increasing clinical recognition.[6, 21-23] The evidence of sensitivity to endogenous endocrines is manifested by many widespread symptoms. These may include certain classic allergic complaints characterized by urticaria or pruritus and may also be evident by premenstrual weakness, nausea and vomiting, migraine headaches, asthma, allergic rhinitis, superficial keratitis and diarrhea. This wide multitude of symptoms comprises the complex commonly encountered in all allergies. The actual demonstration of this specific allergy may be attempted by the use of certain skin testing procedures as follows:

The steroid hormone to be injected or tested is prepared in a nonallergenic oil containing a concentration of 1.0 mg. of the actual material per cubic centimeter of the oil vehicle. One-tenth cubic centimeter of this preparation is injected intradermally. Control injection of the vehicle alone is to be employed and other controls such as the vehicle plus cholesterol can be utilized. Readings of the skin-tested area are made at 24, 48 and 72 hours after the skin test procedure has been performed. A positive test is one showing the following salient findings: There should be an area of induration of some 5 mm. or more. There is usually a surrounding area of erythema. Subjectively the patient may notice marked pruritus at the site of the injection. It is important to note that at times one may not discern a positive reaction unless the patient is seen during the allergic phase of her menstrual cycle; i.e., a patient who has shown evidence of allergy at the time of menses may show a negative skin response to the inciting hormone midway in her cycle. However, when menses occur, the area of the skin test, while done some 2 weeks previously, will become pruritic, will show some erythema and may become indurated. This is evidence, again, of a positive skin reaction and indicative of a definitive sensitivity to the particular inciting steroid allergin.

The patients showing positive skin tests and allergic symptoms, which are severe enough to warrant extensive therapy, are subjected to the following desensitization procedure: They are first treated with a dilute aqueous saline solution of which 1 cc. contains 1000 I.U. of estrogenic substances in aqueous suspension plus 1.0 mg. of progesterone or any other steroid hormone to which the patient may be sensitive. One-tenth cubic centimeter of this preparation is injected subcutaneously per day, and the amount is increased on subsequent days by 0.1 cc. until 1 cc. is received. The injections are given at the rate of 5 times per week. When 1 cc. of the dilute solution is reached, the patient is then placed on the concentrated solution made up as follows: 2000 I.U. of estrogenic substances plus 2 mg. of progesterone or the other steroid hormones that the patient may be sensitive to are suspended in 1 cc. of saline. Here, too, the patient is started on 0.1 cc. and the dose is increased by 0.1 cc. until 1 cc. is reached. Five injections per week are given. On attain-

ment of the 1 cc. dose the patient then receives 1 cc. of the concentrated preparation 3 times a week until she has undergone 2 or more months of desensitization. As a result of this form of therapy, we have found that patients showing marked premenstrual tension or nausea and vomiting, migraine headaches, etc., preceding or associated with the menses have been helped. Obviously this form of therapy should be used only in those patients showing severe symptoms correlated with the menstrual cycle. Patients who at the time of ovulation may complain of severe vaginal pruritus or show marked urticaria may also be effectively treated by the desensitization procedure outlined.

Premenstrual tension of moderate degree, however, may be controlled by less complicated therapeutic procedures requiring the premenstrual administration of one of several of the orally effective steroids or parenteral or oral mercurials exhibiting low toxicity. These methods will be discussed more fully in the section on premenstrual tension.

Androgens and Libido

Libido in the female may be primarily a problem of the psyche. However, there are many women who have once experienced libido but have lost it who may be helped by the judicious use of the proper steroid hormone. It is our opinion and that of others[24] that the clitoris may represent the center of eroticism in the female. Since the clitoris may be stimulated directly by the action of androgens, it has been generally accepted, despite the apparent paradox, that androgens may actually stimulate libido in the female or cause a return when it has been lost. Evidence for this has been manifold.[25-27] It has been noted in patients receiving testosterone for uterine myomas causing menorrhagia.[26] A marked increase in libido has also frequently occurred in patients receiving androgens as palliative measures because of neoplastic disease—an increase far and above that explainable on psychogenic influences. Similarly, the administration of androgens for the treatment of various gynecologic disturbances has been associated many times with an increased libido. Nevertheless it must be emphasized that one can expect little ameliorating effect from the androgens on frigidity in females who have never experienced libido. This latter group of patients must be considered primarily as psychiatric problems.

In contrast to androgens, there are other steroid hormones that may have a depressing action on libido. This has been repeatedly noted in regard to progesterone.[28,29] Of interest is the fact that some patients with nymphomaniac tendencies or those who experience nocturnal orgasm as a result of erotic dreams may have these episodes decreased in extent by administration of progesterone.[30] However, it must be kept in mind that some patients with nymphomaniac tendencies may actually be showing excessive desire for sexual intercourse because of the fact that they have not been able to attain a sexual climax. As a result repeated sexual contact is attempted in order to achieve gratification. In such patients, paradoxically, it may be helpful to administer testosterone. Theoretically it may be argued that such therapy would increase the libidinous feeling. However, the androgen medication may permit the patient to achieve an orgasm and in so doing decrease her desire for frequency of sexual intercourse.[30]

Progesterone Therapy in Diagnosis and Therapy of Amenorrhea

The etiology of amenorrhea may be very simply stated as being due to either pituitary, ovarian or endometrial failure. These may be either secondary or primary—secondary to other disturbances in the endocrine glands or to the psychosomatic make-up of the individual, primary as a result of dysfunction of either one of these structures. As a means of delineating the causative agent in the etiology of amenorrhea, a simple scheme of therapeutic tests with various hormones has been employed to determine which organ may be responsible.[31] Prior to the onset of this diagnostic regimen, it is important that all other endocrine factors be ruled out by complete physical and gynecologic examination. This, of course, would include the detection and treatment of obvious dysfunction of the

thyroid and/or adrenal glands. Obstructive lesions and aplastic congenital anomalies if present should be detected before the patient is subjected to the following work-up.

Patients with primary or secondary amenorrhea are first given 100 mg. progesterone as a single intramuscular injection. Following the injection, one of two things may occur—she may either menstruate or not menstruate. If she does menstruate, it indicates that the patient has had adequate estrogenic activity and implies that there has been a sufficient level of estrogen to stimulate the proliferative phase of the endometrium, thus making it responsive to the action of progesterone. Progesterone cannot induce secretory changes followed by subsequent bleeding unless the endometrium has been adequately primed with estrogens. Withdrawal bleeding after secretory changes have been brought about in the proliferative endometrium occurs promptly after progesterone therapy. Hence it can be concluded that those patients who menstruate after the injection of progesterone must have adequate estrogenic activity and therefore must have sufficient pituitary stimulation or secretion of follicle-stimulating hormone. The stimulation of the ovarian follicles by the pituitary hormones results in the production of estrogens, which in turn have a stimulating effect on the endometrium.

If the patient does not menstruate after progesterone, then we still have not identified disturbances in the pituitary, ovarian or endometrial function as the possible cause of the amenorrhea. The patient who fails to menstruate within 2 weeks after progesterone alone is then given cyclic therapy of estrogen and progesterone. This consists of a 3 week course of estrogen therapy followed by the same dose of progesterone (100 mg.) administered intramuscularly. The choice of the estrogen to be used in the estrogenic phase of the cyclic therapy may lie in any one of several preparations. These may include ethinyl estradiol, 0.05 mg. twice a day for 3 weeks, or conjugated estrogens (equine) 1.25 mg. twice a day for 3 weeks, or the patient may be placed on stilbestrol 0.1 mg. 3 times a day for 3 weeks, or 0.5 mg. dienestrol twice a day for 3 weeks, or 12.0 mg. tri-p-anisyl chloroethylene twice a day for 3 weeks. Any other suitable estrogen may be substituted for these preparations. If a menstrual period does not occur within 2 weeks after the injection of progesterone, one may assume that there must be some form of endometrial failure. In such cases the prognosis is poor. Endometrial failure may be due to any one of several factors which have been outlined in a previous report.[31] Briefly these include failure due to mechanical, radiation or infectious factors or as a result of congenital aplasia. In case menstruation does result, it has been established that endometrial failure is not responsible for the amenorrhea and either the ovary or the pituitary must be considered as the etiologic agent.

To establish the defective role of either the ovary or the pituitary in these patients at this time, one of two things may be done. The patient may be given a course of pregnant mares' serum gonadotropin consisting of 500 I.U. 3 times a week for 3 weeks, following which the patient will either show a response or fail to exhibit any definitive change as a result of this type of therapy. An adequate response to therapy would be characterized by maturation of the vaginal smear, stimulation of the breasts, and menstruation after completion of therapy.

If there is a failure of response, one may assume with reasonable certainty that the ovaries are incapable of being stimulated. This may be due to either primary ovarian failure, ovarian agenesis or refractoriness to gonadotropic stimulation. However, if ovarian activity does occur, as evidenced by the fact that the patient responds to the administered pregnant mares' serum, we then have evidence that the patient has functioning ovaries but that there must be some decrease or abnormality in anterior pituitary activity.

Whether the amenorrhea is caused by ovarian or pituitary disturbances can be further classified by determining the patient's urinary gonadotropic excretion. The gonadotropic excretion study would be essentially corroborative of the observations made after pregnant mares' serum administration. Thus if an in-

crease in gonadotropic secretion over the normal values for the laboratory is noted, one must consider the possibility of ovarian failure or agenesis. The increased gonadotropic excretion implies that there is no inhibition of pituitary gonadotropic secretion by ovarian hormones. This results in increased release of gonadotropic hormones from the pituitary. The role of the ovary in the etiology of the amenorrhea is obvious since more than an adequate amount of pituitary gonadotropin is available without evidence of ovarian stimulation. The futility of additional gonadotropic hormone is apparent in such patients since they already have an excessive secretion of endogenous gonadotropic hormone. On the other hand, if the patient has a decreased or subnormal gonadotropic excretion, then some degree of pituitary failure is present. This is the same type of patient who in all probability will show an effective response to pregnant mares' serum therapy.

Thus by the use of this diagnostic work-up, including the therapeutic application of various hormone preparations, and the performance of a gonadotropic assay one can accurately determine whether pituitary, ovarian or endometrial failure is responsible for the amenorrhea. If there is any evidence of hyperthyroidism or hypothyroidism, control of the thyroid dysfunction by use of antithyroid or thyroid medication should be accomplished. Increased adrenocortical activity, as manifested by hirsutism, abnormal menstrual periods or amenorrhea, and an increased 17-ketosteroid excretion may be very adequately controlled by cortisone therapy in the range of 12.5 mg. 2 to 3 times a day. If the thyroid and the adrenals have been ruled out as contributing factors to the amenorrhea and the pituitary has been indicted, then cyclic therapy with estrogen and progesterone medication based on the same routine used in the diagnostic work-up may be employed. Withdrawal bleeding is induced with this type of hormonal therapy every month for a period of 4 to 5 months, following which all endocrine replacement therapy is discontinued. The patient is then observed for several months to see whether spontaneous menstrual periods will occur. This form of cyclic replacement therapy has proved to be an effective form of treatment of patients with amenorrhea in many instances and may actually institute normal cycles.

Amenorrhea followed by withdrawal bleeding after progesterone administration may indicate that some psychosomatic disturbances are present and several monthly courses of progesterone therapy alone may be helpful in inducing a regularity of menstrual function. In addition to the intramuscular administration of a single dose of 100 mg. of progesterone one may also choose to use oral forms of progesterone medication. These preparations consist of anhydrohydroxyprogesterone given in 10 mg. doses 3 times a day for a period of 7 days. A comparable effect may also be achieved by the administration of progesterone linguets in the form of 25 mg. doses 3 times a day for 5 days. Daily injections of 25 mg. of progesterone per day for 4 to 5 days may also be administered with essentially the same results as a single 100 mg. injection. Progesterone has many other uses in gynecology, and some of these will be discussed under premenstrual tension.

Therapy of Premenstrual Tension or Menstrual Molimina

Premenstrual tension or menstrual molimina of an extent not severe enough to require desensitization or skin testing noted in patients with an endocrine allergy may be treated by the following forms of therapy: If the patient has premenstrual tension not associated with dysmenorrhea, we have found that the administration of a progesterone preparation for a week or 10 days preceding the onset of the expected menstrual period may prove to be effective in controlling all symptoms. The doses used are 10 mg. of anhydrohydroxyprogesterone given twice a day for a week to 10 days preceding the menstrual period. This preparation will markedly ameliorate premenstrual tension. However, if the patient has dysmenorrhea plus premenstrual tension, preovulatory administration of methyltestosterone as described in the treatment of dysmenorrhea may be very helpful.

In some patients the use of progesterone to relieve premenstrual tension will aggravate mild dysmenorrhea. In these patients one should employ methyltestosterone 10 mg. 2 to 3 times a day for the week preceding the onset of the menstrual period. Both of these procedures (preovulatory or premenstrual administration of methyltestosterone) have been associated with a fair degree of success in controlling premenstrual tension or menstrual molimina of a degree not warranting desensitization with a steroid hormone. Cyclic mastalgia alone or associated with premenstrual tension may be controlled very well by using the same dose of anhydrohydroxyprogesterone suggested for menstrual molimina or by 10 mg. of methyltestosterone or 25 mg. of methylandrostenediol given twice a day for a week before the expected menstrual period. Both latter preparations have proved to be equally effective.

Other forms of therapy in premenstrual tension have utilized the principle of increasing water diuresis by the administration of well-tolerated mercurial diuretics given either orally or intramuscularly. These diuretics are reserved for those patients who show evidence of premenstrual tension associated primarily with weight gain and evidence of increased water retention. The oral preparation used has been mercumatilin of which the patient takes 134 mg. per day, equivalent to 40 mg. each of mercury and theophylline, during the week preceding the menstrual period. Sodium mercaptomerin may also be used. It is a parenteral preparation that can be administered subcutaneously in 1 cc. doses containing 40 mg. of mercury on the tenth and fifth days before the onset of the menstrual period. Both of these mercurial diuretics are associated with a low incidence of toxicity and are well tolerated by the patient. Their use has resulted in an adequate therapeutic response.

Use of Cortisone in Control of Menstrual Abnormalities Associated with Increased 17-Ketosteroid Excretion

Recently Wilkins and his co-workers,[32,33] Seegar-Jones, et al.[34] and others (Kupperman, et al.)[35] have shown that the administration of cortisone to women exhibiting adrenal hyperplasia or increased function as manifested by amenorrhea or by irregularity of menstrual cycles, hirsutism and an increased 17-ketosteroid excretion has resulted in amelioration of this condition associated with the resumption of regular ovulatory cycles.

Briefly the indications for the use of cortisone are patients exhibiting an excessive amount of hirsutism, abnormalities in ovulation, and some evidence of increase in masculinization accompanied by excessive 17-ketosteroid excretion in the urine. The administration of small doses of cortisone orally in the range of 12.5 mg. 2 to 3 times a day has produced suppression of adrenocortical activity to a sufficient degree so that normal gonadotropic excretion and ovarian function take place. The *modus operandi* for this form of therapy has been based on the concept that the increase in 17-ketosteroid excretion represents a metabolic breakdown of products of certain androgenic precursors. These are presumably under the control of and induced by increased pituitary ACTH secretion. Since they are present in increased quantities, it has been suggested that they have an inhibiting effect on the secretion of follicle-stimulating hormone from the pituitary gland. As a result a decrease in pituitary-gonadotropic hormone secretion occurs, resulting in complete or partial failure in ovarian function. This is manifested by some irregularity of the menstrual cycle. With the administration of cortisone partial suppression of the pituitary ACTH secretion occurs and as a result a decrease in the ketosteroid precursors is brought about. With the decrease in the 17-ketosteroid precursors, inhibition of pituitary gonadotropic secretion disappears. Consequently a more normal function or activity of the pituitary-gonadal axis is permitted and relatively normal cycles follow.

It is important to emphasize that this form of therapy has proved to be successful only in those cases in which an increased 17-ketosteroid excretion can be demonstrated. One can expect little success in establishing regularity of menstrual cycles with cortisone when pa-

tients show either normal or depressed 17-ketosteroid values in the urine. The menstrual abnormalities associated with increased 17-ketosteroid excretion have been ameliorated or corrected by this cortisone therapy so that patients who had anovulatory cycles prior to therapy have had regular ovulatory cycles subsequent to adequate cortisone administration. Patients with adrenogenital syndrome associated with precocious sexual maturity in the female and accompanied by an increase in the size of the clitoris and the presence of hirsutism not associated with any evidence of precocious menstrual periods have been treated very effectively by the administration of cortisone. Obviously the administration of cortisone plays no role or is of no value in patients in whom constitutional sexual precocity occurs as a result of acceleration in the process of gonadal development by increased pituitary gonadotropic secretion.

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Pediatrics IN GENERAL PRACTICE

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Combined Immunization

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THEORETICALLY, a large number of antigens are available for combined immunization, but if discussion is limited to those suitable for pediatric use which are comparatively free from reaction, the choice is markedly narrowed. The combinations we are now discussing are (1) diphtheria and tetanus toxoid, alum precipitated; (2) diphtheria toxoid-pertussis vaccine, alum precipitated, and (3) diphtheria and tetanus toxoids and pertussis vaccine in fluid (no precipitants), alum precipitated, aluminum hydroxide or aluminum phosphate precipitated forms. A useful preliminary to discussion of these forms is a review of the commonly accepted criteria of immunity to diphtheria, tetanus and pertussis.

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Diphtheria

While the Schick test is a fairly reliable clinical index of immunity to diphtheria, the necessity for a quantitative approach in evaluating the antigenicity of various methods of immunization has led all recent investigators to measure the level of circulating diphtheria antitoxin in the blood. Almost any of the methods of combined immunization produces levels of diphtheria antitoxin in the order of 0.1 antitoxic unit per milliliter of blood to as high as 1.0 unit, far above the so-called "Schick level," which recent estimates have calculated as ranging from 0.004 to 0.01 antitoxic unit per milliliter. Such high levels are considered advisable because it seems reasonable to assume that, in some countries, strains of diphtheria bacilli exist which are capable of producing the disease in individuals with antitoxic titers above 0.01 unit per milliliter of blood. High levels may then prevent epidemics of the so-called malignant diphtheria, perhaps caused by the Gravis type of bacilli, which occurred in Germany and other European countries and which often failed to respond to antitoxin.

The optimal age for diphtheria immunization is still under discussion. While clinical diphtheria is rare in this country in infants

under 6 months of age, the past decades have witnessed an astounding decline in the percentage of pregnant women who are Schick-negative, due to lack of subclinical immunization, and therefore we must expect less and less transplacental transfer of diphtheria antitoxin. For this reason, even though this temporary transplacental passive immunity may interfere somewhat with the production of active immunity, we no longer object to starting immunization as early as 3 months of age.

The optimal toxoids to be employed, it has been pointed out, should be those producing the highest possible antitoxic level without harmful reaction. A certain percentage of children, so-called "poor antitoxin producers," may have titers of less than 0.001 unit per milliliter at the time of the booster dose, and respond less well than those with titers above this level. By using the precipitated toxoids—alum, aluminum hydroxide or aluminum phosphate—the immunization program secures an initially high level of antitoxin, and by a booster dose one year later, and at regular periods thereafter, prevents the level from falling below 0.001 unit per milliliter.

Since subclinical infections are no longer present to stimulate a prolonged active immunity, booster or stimulating doses at 2 year intervals will, in all probability, have to be continued almost into adult life. As children grow older, the number sensitive to diphtheria toxoid rises rapidly, so that large booster doses—in the order of 15 to 40 Lf—will produce severe reactions in a substantial proportion. In these older children and adults, the use of fluid diphtheria toxoid of the "purified" type, together with a Maloney test for toxoid sensitivity, will be necessary.

Tetanus

The problem of tetanus immunity differs from that of diphtheria, because there is no natural immunity, no subclinical infection, and no simple test comparable to the Schick test. The time-honored standard dose of 1500 units of tetanus antitoxin for passive prophylaxis, resulting in an antitoxic level of 0.01 to 0.1 unit per milliliter of blood at the end of 2 weeks, may protect against minor infections, but complete protection in actively immunized guinea pigs is associated with antitoxic levels of 0.2 to 0.5 unit per milliliter of blood. Therefore with tetanus, as with diphtheria, the wisdom of attaining levels of 0.1 up to 1.0 unit per cubic centimeter in routine immunization forces the employment of the precipitated toxoids.

The optimal age for tetanus immunization is not important, since cases in early infancy are very rare, and since there is no transplacental transfer to interfere with the production of active immunity. In a combined program, the 3 month period selected for diphtheria and pertussis may be allowed to govern.

The need for attaining and maintaining at all times as high as possible a level of tetanus antitoxin becomes evident from the fact that 60 per cent of clinical tetanus cases follow no history of injury or an unimportant injury. For this reason, a booster dose of precipitated toxoid a year later, and an "emergency" dose of fluid toxoid after any injury are now widely recommended. U.S. Army and Navy results with this procedure have been so strikingly successful that the British Army recently abandoned its practice of giving so-called active-passive immunization after trauma, i.e., the simultaneous injection of toxoid and prophylactic antitoxin. Whether this should apply in the exceptional cases of extensive trauma or massive contamination, characterized by short incubation periods and a high fatality rate, is not yet certain, since some individuals are notoriously poor antitoxin producers in tetanus as in diphtheria. For the "emergency" dose on injury, the arguments for the speedier absorption of the fluid toxoid as compared with the precipitated type seem quite conclusive. The absorption of toxin from a wound is apparently insufficient to stimulate the rise in serum antitoxic level to an immune level, and should never be depended on to the exclusion of the emergency dose of toxoid.

Pertussis

Active immunization against pertussis, employing a fluid vaccine prepared on a Bordet-

Gengou medium enriched with human, bovine or sheep blood in a total dosage of 80 to 100 billion organisms, proved its value in extensive tests of clinical exposures. Since then, it has become evident that strains of *Hemophilus pertussis* differ tremendously in their ability to evoke antigenic responses, and practically all manufacturers have changed to potent strains of *H. pertussis* grown on synthetic liquid mediums. The use of adjuvants, like precipitation with alum or aluminum hydroxide and aluminum phosphate, seems to enhance the antigenic stimulus by a slow release of antigen. There has been no conclusive proof, such as tests of clinical exposures, to prove that the use of precipitated pertussis vaccines will afford substantial immunity with doses less than the 80 to 100 billion figure given for the fluid vaccine. Serologic tests for agglutination reactions with a titer of 1:320 or more are usually associated with immunity and the manufacturers base their claim that total doses of 45 billion of the precipitated vaccines will produce immunity on such indirect serologic evidence.*

The optimal age for immunization against pertussis is conditioned by the relative inefficiency of young infants in achieving high titers of agglutination reactions against *H. pertussis*, as well as the fact that two-thirds of the mortality from pertussis occurs before the age of 7 months. For this reason, the trend has been to immunize at lower and lower ages, some even at birth. It must be emphasized that there are no reports of extensive series of clinical trials of infants made immune at such an early age, that the percentage achieving high titers is distinctly lower than at later ages, and that the recent figures for pertussis mortality and morbidity have changed strikingly. Thus, in the city of New York, with a population close to 8 million, in districts where immunization is started at 3 months of age up to 9 months of age, the Department of Health reported only 1 death from pertussis in 1951.

A factor making many of the disagreements on the optimal age for starting immunization only academic is the almost universal practice of booster doses, often given 6 months after the initial immunizations. This should compensate for the antigenic inefficiency of the very young infant. Another factor will be discussed under the paragraph on reactions.

Vaccine Combinations

The diphtheria-tetanus toxoid combination in alum-precipitated form has been shown to give higher antitoxin titers, maintained over a longer period, when 3 injections of 1 cc. each were used at 4 to 5 week intervals than the fluid toxoids, in combination, or the antigens singly employed. However, the antitoxic levels resulting from the double mixture are distinctly lower than those resulting from the triple mixture, if due weight is given to the percentage of cases reporting really high levels, 1.0 unit and over.

The diphtheria toxoid-pertussis vaccine combination, either fluid or alum precipitated, achieved a vogue for a time, but the levels attained were not as high as with other double combinations or with the triple combination. The questions of the duration of immunity with this combination, the need for booster doses, and the avoidance of reactions do not seem to have been thoroughly settled.

The triple combination of diphtheria and tetanus toxoids with pertussis vaccine has been used in fluid mixtures and in mixtures precipitated with alum, with aluminum hydroxide and with aluminum phosphate. A comparison of a fluid triple mixture containing 100 billion of *H. pertussis* with an alhydrox mixture containing only 50 billion showed that the antitoxic levels for diphtheria and tetanus, and the percentage of cases attaining a pertussis-agglutinating titer of 1:320 (considered protective), were substantially the same. The results with the alhydrox triple mixture are for the most part markedly supe-

*Since August 1, 1953, the label on pertussis vaccine no longer indicates bacterial count per cubic centimeter. The National Institutes of Health request instead a statement of the number of protective units for one total human immunizing course. The requirement for a total immunizing dose is 12 units. Laboratories are requested to test their pertussis vaccine potency against a standard vaccine with a designated number of protective units using the mouse protective method.

rior to those obtained with single immunizations, or to the results for the double mixtures mentioned above.

Some years ago, alum abscesses, perhaps caused by the low *p*H of the alum combined with the necrotizing power of *H. pertussis* vaccine, became a serious deterrent to the use of these mixtures. Deep intramuscular administration, avoidance of intracutaneous soilage, holding the needle downward, finishing off the injection with 0.1 cc. of air, and using the buttocks were all recommended to obviate this difficulty, but controlled studies were not convincing. Since the new regulations of the National Institutes of Health, forbidding the use of more than a small amount of alum, no abscesses have been encountered, although a local node is often felt for months. The use of aluminum hydroxide was a real improvement and recently adsorption on aluminum phosphate has been reported favorably by Watson and Stewart at the University of Michigan.

Reactions to Combined Vaccines

The reactions to diphtheria and tetanus toxoids with the use of refined toxoids are so mild in young infants that they can be disregarded. In older children and adults local and systemic reactions occur more often.

On the other hand, pertussis vaccine causes local reactions consisting of redness, swelling, induration, regional adenitis, and occasionally ecchymotic areas. In addition, the alum frequently causes harmless nodule formation, and, formerly at least, produced sterile "alum cysts" in a small percentage. Pain and subfebrile temperatures are observed in 10 to 40 per cent of the children. Fever may reach 104° F. or so, but rarely, if ever, persists for more than 36 hours. A dangerous possibility is pertussis vaccine encephalopathy with convulsions, hyperpyrexia, irritability or drowsiness, mental deterioration, and, in a number of cases, fatalities. Since no new reports have appeared since 1949, it seems possible that the change in the preparation of the vaccine from a solid to a synthetic fluid medium and the new N.I.H. requirements for aging of the vaccine, proper strain selection and proper animal testing have diminished the possibility of this dangerous reaction. However, it should be emphasized that no child who has had convulsions in the past, or is ill in any way when seen, should receive the usually recommended doses of the triple mixture.

Recently a possible relationship between recent immunization and the site of paralysis in poliomyelitis has been postulated in this country and abroad. The question remains whether in these cases a pre-existing infection becomes exacerbated and localized or whether paralysis in an inoculated limb may be due to the accidental introduction into peripheral nerves of virus from the patient's own skin or from previously contaminated needles and inadequately sterilized syringes. Whether the injection of immunizing antigen really caused the paralysis or whether their occurrence was purely coincidental is likewise debatable.

The Bureau of Preventable Diseases of the New York City Health Department stated in 1952 that there is no evidence that there is an increase in the numbers paralyzed as a result of inoculations. "The results of failing to immunize children against diphtheria, tetanus and whooping cough could be much graver than the possible chance of an increase in poliomyelitis. The Department of Health will, therefore, continue the immunization of infants and children in its child health stations throughout the summer."

However, it is clearly wise to accept Faber's recommendation that in the polio season needles and syringes should be boiled and iodine used as the skin antiseptic. Also it may be advisable to postpone routine immunizations when the local incidence of polio is high.

Practical Recommendations for Immunization

Start monthly injections of triple antigen at 3 to 4 months of age, giving 3 to 4 injections of 0.5 cc. each for a total of 45 to 60 billion pertussis organisms. A total of 30 billion organisms, which is still recommended by many manufacturers, appears inadequate clinically. In order to avoid reactions, we start with 10 billion *H. pertussis* and increase to

20, 30 and 40 billion as desired. Booster doses of 0.5 cc. of the triple antigen should be given at the age of 12 to 18 months, at 2½ to 3½ years and before entering school.

To avoid reactions, doses should be individualized. Never inject an ill child, because the injection may act as a trigger mechanism in producing convulsions. Clinically, reactions in young infants seem fewer, reactions less common and very few cases of encephalopathy have been reported in this age group. If there has been a marked febrile or other untoward reaction from any injection, the next dose should be cut sharply. If convulsions or hyperthermia or drowsiness is reported, no further pertussis vaccine should be given. In a few children it was necessary to discontinue pertussis vaccine due to marked reactions with very small doses. Although we believe that encephalopathy is probably on an allergic basis, there seems no clinical reason to discontinue administration of triple antigen in allergic children.

Addendum

The recent literature on combined immunization applied to adults is scant. Reactions have been frequent and severe, but Ruegsegger and Loeser,[1] using alcohol-refined diphtheria and tetanus toxoids in 31 adults, noted fewer and less severe reactions. The stimulation of adequate and durable immunity was confirmed by serial antitoxin titrations. Although many authors have recommended intracutaneous administration, in our experience the intramuscular route has been safer. In general the use of pertussis vaccine does not seem necessary for adults, but combined diphtheria-tetanus toxoids should be useful both for basic immunization and for stimulating doses.

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Prevention of Rheumatic Fever and Rheumatic Heart Disease

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New York University College of Medicine, New York City

In recent years rheumatic fever has received considerable publicity as a public health problem. Progress has been made in the field of prevention and new prophylactic procedures are now available.

Prevention of Rheumatic Recurrences

In individuals known to have had rheumatic fever or chorea, the physician's chief concern is the prevention of recurrences. It is now well established that by protecting rheumatic subjects from streptococcal upper respiratory infections, the incidence of rheumatic recurrences can be greatly reduced.[1-5]

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Although, in contrast to polyarthritis and carditis, evidence that chorea is preceded by streptococcal pharyngitis is often lacking, many patients with so-called "pure" chorea subsequently develop other manifestations of rheumatic fever. These individuals, therefore, should also receive prophylactic medication. At the present time 3 different drugs are commonly used for this purpose.

1. *Sulfonamide drugs*—Sulfadiazine in a daily dosage of 0.5 gm. for individuals weighing less than 60 pounds and 1 gm. for those weighing more than 60 pounds has been most widely used. Some of the new sulfonamide drugs, however, are probably equally effective. Sulfonamide prophylaxis can usually be started during convalescence from an acute rheumatic attack. Sulfa-resistant strains of

group A *Streptococcus* were encountered in the Armed Forces during World War II, but have been extremely uncommon in civilian populations.

Toxic reactions occur, but are infrequent. Toxic rashes may develop, usually during the first 2 weeks. If an erythematous morbilliform eruption occurs the sulfonamide should be omitted for a few days and then may be restarted cautiously, provided the patient is under close supervision. Often no further skin manifestations develop and the patient is able to tolerate the drug for years without difficulty.

The appearance of urticaria, on the other hand, is a definite indication that sulfonamides should be permanently discontinued. In such individuals, if the drug is stopped and restarted a more severe reaction often occurs after a shorter interval.

Because of the danger of agranulocytosis, it is advisable to do leukocyte counts at weekly intervals for the first 6 weeks. If the white blood count falls below 4000 cells with less than 35 per cent polymorphonuclear neutrophils, the drug should be discontinued. Sulfonamide prophylaxis may be restarted cautiously and in some instances leukopenia does not recur.

If, while on sulfonamide prophylaxis, the patient develops fever and a sore throat or other signs of infection, the symptoms may be associated with leukopenia. Even if the leukocyte count is normal or elevated, it is usually not advisable to increase the dosage of the sulfonamide. In such cases antibiotic therapy is preferable.

2. *Oral penicillin*—Fewer controlled studies have been done with oral penicillin than with the sulfonamide drugs. However, the evidence that has been accumulated indicates that oral penicillin is a safe and effective prophylactic agent. So far, no penicillin-resistant strains of group A hemolytic streptococci have been reported. Oral penicillin is particularly useful for patients who cannot tolerate sulfonamide drugs.

Oral penicillin rarely causes toxic reactions. Occasionally urticaria develops. In most instances if penicillin is stopped for a few days, it can be restarted without causing further difficulty. If, however, the urticarial reaction has been severe and accompanied by angioneurotic edema, penicillin should be permanently discontinued.

Penicillin tablets buffered with calcium carbonate give satisfactory serum levels only if ingested under fasting conditions.[6] Recent studies using penicillin buffered with sodium citrate, on the other hand, indicate that these tablets are well absorbed irrespective of whether they are taken before or after meals.[7] Since very few patients can be relied on to take medication regularly half an hour before breakfast, oral penicillin tablets buffered with sodium citrate are recommended.

3. *Repository pencillin:* BICILLIN® *by injection*—The chief difficulty with any daily prophylactic medication is that ambulatory patients are apt to forget to take the tablets regularly. Recently a new repository penicillin, NN′ dibenzylethylenediamine dipenicillin G (Bicillin by injection) has been developed. A single intramuscular injection of 1,250,000 units of this compound once a month will insure adequate prophylactic serum levels. The site of injection tends to be somewhat more painful than with procaine penicillin, but no serious reactions have been observed.[8]

Which of these 3 types of prophylactic medication to use will vary with the individual. Some mothers can be relied on to make sure that the tablets are taken daily without fail. Others may think it easier to bring the child to the doctor's office or clinic once a month for an intramuscular injection of Bicillin. Because the potential danger of serious organic heart disease increases with each rheumatic recurrence, it is recommended that prophylaxis be maintained continuously summer and winter until the patient is 18 years of age. In older individuals it should be continued for 5 years after the most recent attack.[9]

Although every patient who has had rheumatic fever should be protected from recurrences of this disease, it is equally important not to prescribe years of medication to individuals who are not really rheumatic. The manifestations of rheumatic fever are so var-

ied that diagnosis is often difficult. Clear-cut cases of migratory polyarthritis with swelling and tenderness of more than one joint (with or without redness), unequivocal chorea and carditis are usually easily recognized. Minor manifestations suggesting rheumatic fever but not pathognomonic, such as "growing pains," arthralgia occurring simultaneously with upper respiratory infections, epistaxis, erythema multiforme, pallor, fatigability, low grade fever, and abdominal pain, should be carefully evaluated before the patient is labeled rheumatic. It is advisable to keep children with vague complaints of this kind under observation for a considerable period of time. In many instances the symptoms do not recur, or are found to be due to causes other than rheumatic fever. In others unequivocal rheumatic manifestations develop which enable the physician to make a definite diagnosis.

The decision to start prophylaxis for a period of years is a serious one and entails the possibility of causing psychic invalidism unnecessarily in individuals who are not really rheumatic. Less ultimate harm will be done by the occasional failure to recognize the rheumatic whose diagnosis cannot be firmly established.

Prevention of the Initial Attack of Rheumatic Fever

Evidence has been accumulating not only that recurrences of rheumatic fever occur, but also that the initial attack of this disease can be prevented.[10] In studies conducted in the Armed Forces, it has been found that if scarlet fever or streptococcal upper respiratory infections are treated shortly after onset with large doses of penicillin for a period of 7 to 10 days, the incidence of rheumatic fever is greatly reduced.[11]

Scarlet fever is easily recognized. Severe cases of streptococcal pharyngitis, characterized by fever, sudden onset with pain on swallowing, tender cervical nodes and exudate on the tonsillar area, in most instances also offer no difficulty. For such cases intramuscular injections of 300,000 to 600,000 units of procaine penicillin and 600,000 units of Bicillin are recommended to eliminate the streptococci from the throat rapidly and prevent their reappearance.[12] The success of this treatment depends on early diagnosis and the maintenance of a prophylactic level of penicillin for a period of 10 days. To prevent the occurrence of secondary cases, household contacts less than 18 years of age should also receive an intramuscular injection of 600,000 units of Bicillin.

For the treatment of acute streptococcal pharyngitis in individuals known to be sensitive to penicillin, AUREOMYCIN® is recommended: 10 mg. per pound of body weight daily for 2 days followed by 5 mg. per pound daily for 8 days. Sulfonamide drugs suppress but do not eliminate streptococci and therefore should not be used.

Unless facilities for demonstrating hemolytic streptococci by throat culture are available, mild cases of streptococcal upper respiratory infection may be missed. However, the data now on hand indicate that the incidence of new cases of rheumatic fever will be reduced if the therapy previously outlined is followed in patients in whom the clinical symptoms and signs suggest the possibility of streptococcal pharyngitis. Simple coryza, cough, hoarseness and tracheitis are rarely due to streptococci.

In spite of the fact that prompt treatment of acute streptococcal infections is effective in preventing rheumatic fever, continuous prophylaxis is preferable in known rheumatic subjects. Rheumatic recurrences often occur following very mild streptococcal infections. The symptoms may be so slight that the patient fails to notify the physician.

At the same time, it must be borne in mind that occasionally a rheumatic patient, either because of failure to take his prophylactic medication regularly or because of an unusually severe exposure to group A hemolytic streptococci, may contract an obvious streptococcal pharyngitis. Such patients should, of course, receive intensive penicillin therapy as outlined.

Conclusion

By treating streptococcal pharyngitis promptly with adequate doses of penicillin,

and by maintaining continuous prophylaxis in known rheumatic individuals of school age, the incidence of rheumatic fever and rheumatic heart disease can be markedly reduced.

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Female Sterility

RITA S. FINKLER AND SYLVIA F. BECKER

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1. A statistical analysis of 405 infertile couples is presented.

2. In this group, 297 cases were due to faults in the female partner and 108 to the male partner. In 32 couples faulty function of generative organs was found in both partners.

Female sterility: 297 cases.

a. Primary ..... 175 cases

b. Secondary ..... 122 cases

3. Female infertility was due to 2 major etiologic factors:

a. Pelvic organic disease ..... 192 cases

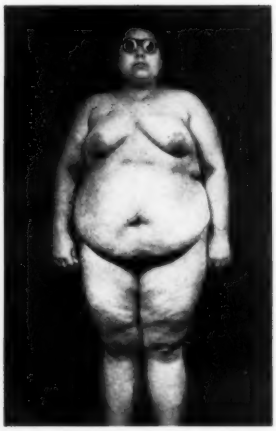
b. Functional disturbances ..... 105 cases
(Endocrine imbalance and psychogenic factors)
Combined factors were also present in this group and could not be definitely separated.

4. Standard diagnostic procedures are outlined.

5. Therapeutic approach to the problem of sterility and infertility is outlined.

ETIOLOGY

OBESITY, EMACIATION AND NUTRITIONAL IMBALANCE

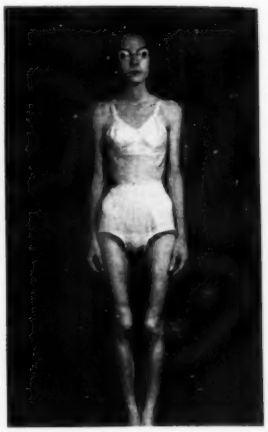


A. OBESE

NUTRITIONAL

A. In obesity, estrogens are frequently stored in fatty tissue, disrupting normal pituitary-ovarian relationship and causing menstrual disturbances and sterility.

B. Malnutrition, particularly protein starvation, inhibits the function of all endocrine glands.



B. EMACIATED

CONSTITUTIONAL

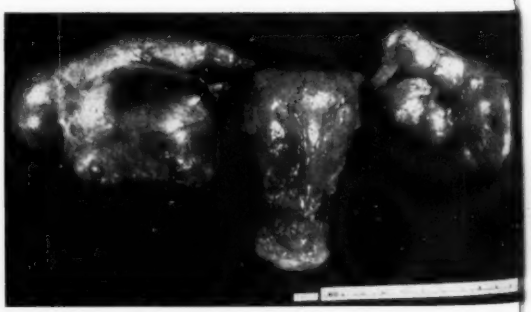
Constitutional diseases such as diabetes, tuberculosis, anemia, syphilis and other debilitating diseases may disrupt pituitary-ovarian-uterine physiology.

Incidence of abortion is increased in these diseases.

PELVIC PATHOLOGY

A. CERVICITIS

Organic pelvic diseases constitute the most frequent cause of sterility. Of 297 cases of female sterility, 192 were due to organic pathology.



B. TUBO-OVARIAN PATHOLOGY

PSYCHOLOGIC

Functional sterility may be caused by juvenile or marital conflicts. If unresolved, disruption of the pituitary-ovarian relationship occurs, inhibiting ovulation in susceptible individuals. This state is usually transitory and curable under favorable conditions.

ENDOCRINE ETIOLOGY

THYROID

A. Thyroid deficiency causes a general slowing down of metabolic processes of the organism. If marked, it is a frequent cause of sterility and habitual abortion.

B. Thyroid overactivity (thyrotoxicosis) may or may not interfere with fertility.

A. DEFICIENCY

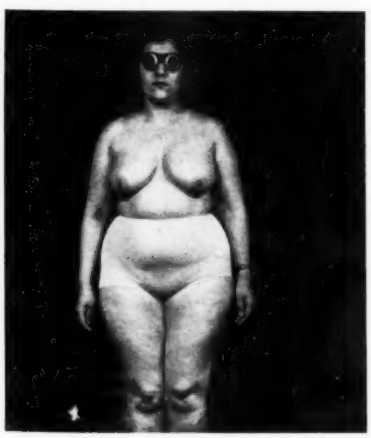
B. EXCESS

PITUITARY

The normal secretion of the pituitary gonadotropins (follicle-stimulating and luteinizing principles) is essential to initiation and maintenance of normal ovarian function.

A. Deficiency in these elements causes menstrual disturbances and sterility.

B. Pituitary overactivity (adenoma) may or may not disrupt ovarian function.



A. DEFICIENCY

B. EXCESS

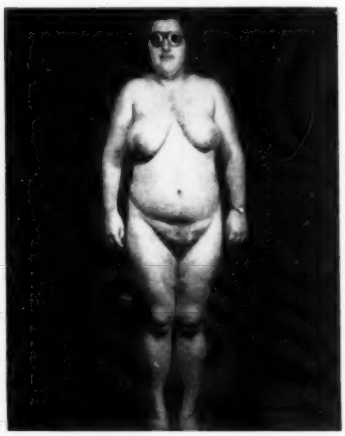
ADRENAL

Diseases of the adrenal gland, namely, Addison's disease (deficiency) and Cushing's syndrome (excess), may or may not interfere with normal menstrual function and fertility.

A. In Addison's disease the general debility depresses the function of the pituitary gland.

B. In Cushing's syndrome the excessive production of the adrenocortical hormones may inhibit pituitary gonadotropic secretion.

A. DEFICIENCY



B. EXCESS

OVARIAN

A. Ovarian deficiency may be primarily due to developmental faults or secondarily due to constitutional, nutritional, endocrine or psychogenic factors. Any interference with normal ovarian physiology may cause permanent or transient sterility.

B. Organic disturbances, particularly cystic ovaries, are frequently encountered.

A. DEFICIENCY

B. CYSTIC OVARY

DIAGNOSTIC TESTS

HUHNER TEST

The Huhner test yields information as to postcoital sperm activity in the vagina and cervix by determining the number of sperms, their morphology and rate of migration.

VAGINAL AND CERVICAL *p*H

Normal vaginal *p*H ..... 4.0 ..... 4.5
Normal cervical *p*H ..... 7.0 ..... 8.5
Increase or decrease in these values occurs in vaginal and cervical infections and may constitute a barrier to sperm penetration.

RUBIN TEST

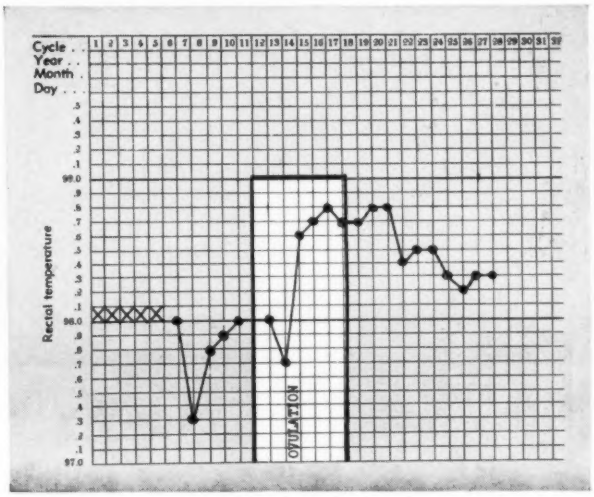
Uterotubal insufflation is carried out routinely.

Various apparatus with kymograph attachments, using carbon dioxide gas, are available.

Dr. I. C. Rubin performing a uterotubal insufflation.

BASAL TEMPERATURE

Daily temperature graphs are recorded covering several cycles. A biphasic graph usually indicates ovulation and progestational activity. The test is valuable and easily carried out but is subject to errors and can be used only in conjunction with other tests.

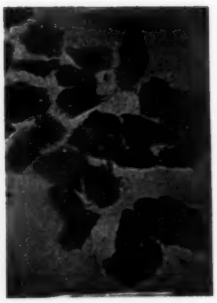


November 1953

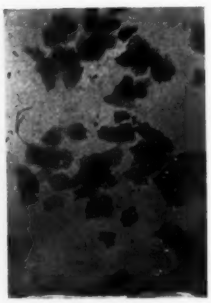
DIAGNOSTIC TESTS

VAGINAL SMEARS

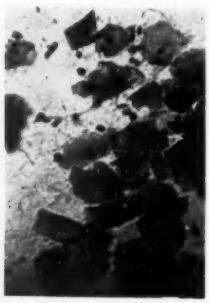
Daily vaginal smears (Papanicolaou and Schorr staining technic) aid materially in the study of ovarian physiology: estrogen production, ovulation and progestational activity.



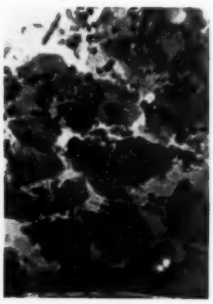
POSTMENSTRUAL



PREOVULATORY



OVULATORY



POSTOVULATORY

PREMENSTRUAL

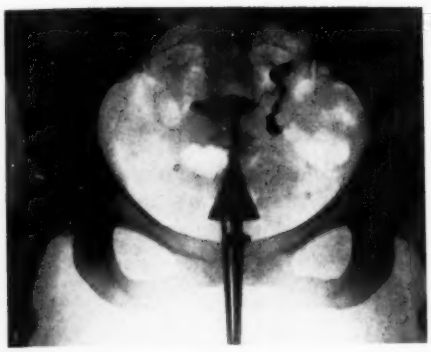
HYSTEROSALPINGOGRAPHY

The roentgenographic visualization of the uterine cavity and the fallopian tubes by means of injection of contrast media (LIPIODOL®, RAYOPAKE®, SKIODAN® Acacia, etc.) is now widely used and may reveal the nature of pathologic processes in these organs. Endocervicitis is frequently demonstrated.

BILATERAL TUBAL PATENCY

DIAGNOSTIC TESTS

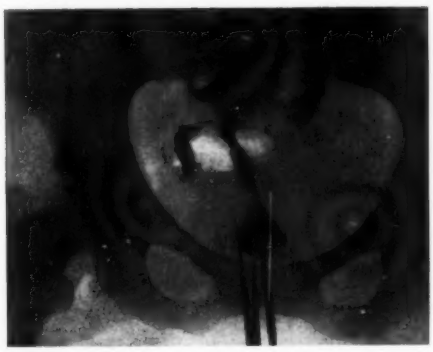
TUBAL OCCLUSION



UNILATERAL

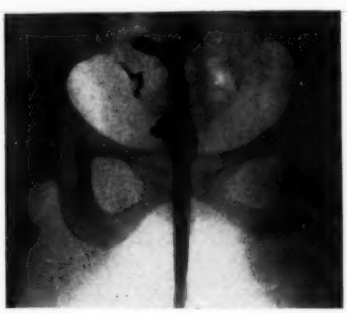
BILATERAL

HYDROSALPINX

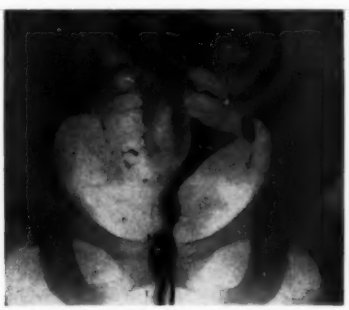


TUBERCULAR SALPINGITIS

UTERINE FIBROID



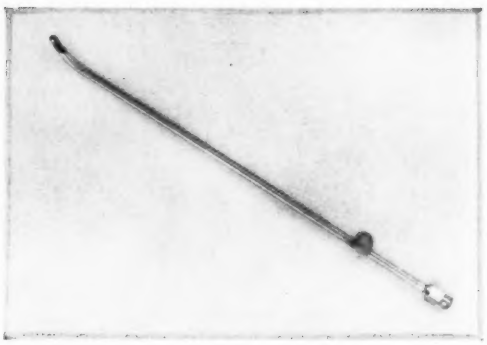
BICORNATE UTERUS



CHRONIC CERVICITIS

DIAGNOSTIC TESTS

ENDOMETRIAL BIOPSY



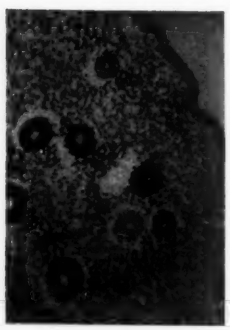
Cyclic changes in the endometrium reflect cyclic ovarian activity. Histologic study of the endometrium offers valuable information pertaining to ovarian function.

Endometrial biopsies are carried out premenstrually or within 24 hours of the onset of menses.

In cases of prolonged secondary amenorrhea more frequent biopsies are indicated. The normal endometrial pattern shows cyclic endometrial growth, as illustrated.

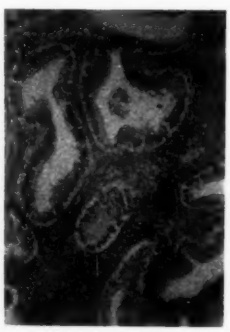
THE NOVAK BIOPSY SUCTION CURET

NORMAL HISTOLOGY



EARLY PROLIFERATIVE

LATE PROLIFERATIVE



EARLY SECRETORY

LATE SECRETORY

NUMBER OF ENDOMETRIAL BIOPSIES PERFORMED	165	Percentage
1. Ovulatory pattern (late secretory)	85	51.5
2. Unovulatory pattern (proliferative)	26	15.7
3. Irregular pattern	54	32.8
a. Endometrial hyperplasia	21	
b. Cystic endometrial hyperplasia	2	
c. Polypoid endometritis	4	
d. Atypical pattern	4	
e. Atrophic endometrium	1	
f. Progestational deficiency (early secretory)	16	
g. Mixed-type endometrium (hyperplastic in secretory phase)	6	

HORMONAL THERAPY

THE GONADOTROPINS

The gonadotropins employed were those obtained from the anterior pituitary gland (pituitary gonadotropins), from the serum of pregnant mares (equine gonadotropins) and from human pregnancy urine (chorionic gonadotropins).

HAMBLEN TECHNIC

Equine gonadotropin (Equinex) 500 to 1000 I.U., 4 to 10 injections during first half of cycle. Chorionic gonadotropin (A.P.L.) 500 to 1000 I.U., 4 to 6 injections during second half of cycle.

RYDBERG TECHNIC

Equine gonadotropin 3000 I.U. for 5 daily injections after period followed by chorionic gonadotropin 1500 I.U. every other day for 3 injections.

Total number treated with hormones.

Therapy	Cases	Conceptions	Miscarriage
The gonadotropins (Pituitary, equine and chorionic)	53	17 (32%)	1

THE STEROIDS

The steroid compounds employed were the estrogens, progesterone and testosterone.

Therapy	Cases	Conceptions	Miscarriage
The steroids	31	9 (29%)	3

THYROID

In our series of cases metabolism tests were carried out on all patients but only 18 could be considered as definitely hypothyroid and responsive to thyroid therapy.

Therapy	Cases	Conceptions	Miscarriage
Thyroid	18	5 (27%)	0

RADIATION THERAPY

In the last 10 years 98 of our patients received pituitary and ovarian irradiation for relief of sterility, as shown in the table below. (Kaplan technic employed.)

RADIATION THERAPY IN FUNCTIONAL STERILITY

Number of cases treated: 98.

Age	Duration of Sterility	Conceptions	Multiple Conceptions	More than 1 living child	Miscarriage
21-40 (Average: 28 yrs.)	1-8 yrs.	41 (42%)	7 (7%)	6 (6%)	6 (6%)

Time interval between termination of therapy and diagnosis of pregnancy: 2 to 8 months (majority 2 to 4 months).

Because of the controversial status of radiation therapy, it is best to attempt, at first, the correction of functional sterility by hormonal therapy and psychotherapy when indicated.

SURGICAL THERAPY

Conservative surgery is attempted in all cases of pelvic pathology in which salvaging of organs is possible. Among these procedures the following have been most commonly employed: enucleation of uterine myomas, correction of uterine malposition and of cervical stenosis, dilation and curettage, removal of endometrial and cervical polyps, lysis of peritubal adhesions and reconstructive tubal surgery and resection of cystic ovaries.

PSYCHOTHERAPY

The approach to the sterility problem from the psychosomatic point of view is rapidly gaining the approval of the medical profession. In some of the infertile couples the marital maladjustment, the anxieties, fears, frustrations and resentments inhibit ovulation or cause tubal spasm. Adjustment of these difficulties often corrects infertility.

CLINICAL STUDY

Hypermenorrhea Due to Scurvy

GEORGE E. MORRIS*

Tufts College Medical School, Boston

This article deals with abnormal menstrual bleeding caused by lack of vitamin C in the blood. Four cases are cited of girls who had positive tourniquet tests and of whom 2 had low blood vitamin C levels. The abnormal menstrual bleeding became normal following the intake of vitamin C and citrus juices.

GEORGE E. MORRIS

A REVIEW of some of the standard textbooks of gynecology and obstetrics[1-3] and of biochemistry[4,5] shows that little reference has been made to the role that vitamin C may play in the cause of menstrual bleeding. Diddle[6] fails to mention the use of vitamin C in the treatment of uterine hemorrhage. Curtis and Huffman[1] state that "Vitamins B, C and K in the treatment of uterine bleeding are in the experimental stage."

Vitamin C deficiency in the adult is commonly reflected in hemorrhages into the skin (usually as perifollicular petechiae of the lower extremities), as hemorrhages into the muscles, or as disease of the gums and anemia. Bleeding from the gastrointestinal tract has been reported, but I am aware of no study, other than that of Stander, et al.,[7] which states that scurvy is a cause of abnormal uterine bleeding. This is a report of 4 such cases that were uncovered during a study of 60 patients with acne; they were found either by detailed history taking or by laboratory methods, and were confirmed by follow-up study.

*Assistant Clinical Professor of Dermatology, Tufts College Medical School, Boston, Massachusetts.

Report of Cases

Case 1—The patient, an 18 year old girl, was seen for an insurance company because of a rash on her hand caused by the use of solvents at work. On her second visit, she showed two hemorrhagic scratch marks on the arm, and inquired as to what they might be (Figure 1).

Such hemorrhagic scratch marks are telltale evidence of vitamin C deficiency. Accordingly, a tourniquet test was performed, which was markedly positive, and the blood vitamin C level was shown to be 0.4 mg. per 100 cc. (Normal: 0.6 to 2.5 mg. per 100 cc.[5]) On questioning whether the patient had experienced any bleeding, she stated that for the past 10 months she had been receiving regular injections from her physician for menstrual bleeding of an excessive nature. She mentioned that the duration of her periods had been 8 days each month, and that these in-

jections had lessened neither the flow nor the duration of her monthly bleeding. She was asked about her diet, and stated that she never ate citrus fruit or drank citrus juices. She was told to drink these fruit juices, and was given 300 mg. of vitamin C a day. Within 3 weeks her menstrual periods were cut to 4 days, and have remained so for over a year while she has been taking this medication. The injections from the other physician were discontinued as soon as she was given vitamin C. She now considers her menstrual periods to be normal, and stated that this is the first time in seven years that they have been so.

Case 2—A student nurse, who was being treated for acne, was given large doses of vitamin C and was told to take an 8 oz. glass of citrus juice twice daily. After receiving this medication for 3 months, she was asked if there had been any change manifested relative to her menstrual periods. She stated that previously her periods had always lasted 6 to 7 days, necessitating the use of 5 to 6 pads a day, but that, since taking the vitamin C tablets, her menstrual periods had been reduced to 3¼ to 4 days, and that she used only 4 pads a day at most. At the time she was placed on this treatment a tourniquet test was taken, which was positive, and her blood vitamin C level was 0.55 mg. per 100 cc. A repeat blood vitamin C level, taken after 3 months, was 2.9 mg. per 100 cc.

Case 3—Another girl, aged 23, had been treated for acne. On her return for a follow-up, she was started on vitamin C and citrus juices experimentally to see if they would improve her complexion, and at the same time she was asked the length and amount of her menstrual bleeding. She stated that her periods lasted from 8 to 9 days and that she had to use 7 or 8 pads a day. Both she and her mother thought that she bled profusely; the mother had wanted her to seek medical advice in regard to the condition, but she had never done so. A tourniquet test proved to be markedly positive; her blood vitamin C level was 1.4 mg. per 100 cc. She was given 4 gm. of vitamin C a day, inasmuch as her next expected menstrual period was within 5 days. This period lasted 6 days. She was continued on 3 gm. of vitamin C daily, and the following period lasted 5 days. She and her mother then affirmed that this was the first time in the girl's life that her menstrual period had lasted only 5 days, and also that there was noticeably less bleeding. Another significant fact is that all previous periods had been at 24 day intervals, and this was her first 28 day interval. On this visit, the blood vitamin C level had risen to 2.5 mg. per 100 cc.

FIGURE 1. Hemorrhagic scratch marks on arm of patient in case 1—evidence of vitamin C deficiency.

The patient was discharged and was told to continue drinking fruit juices. Nine months later, she returned because the acne condition had worsened again. She had not been taking vitamin C, but had been drinking approximately 8 oz. of citrus juice a day. She stated that her menstrual periods had again lengthen-

ed to 8 or 9 days, and that they had been accompanied by profuse bleeding. She was given vitamin C at this time, in dosage of 1.5 gm. per day, and within 2 weeks she experienced a normal menstrual period. She has continued to take the vitamin to the present time without return of either the profuse or prolonged bleeding.

Case 4—A 32 year old doctor's daughter was treated for acne. She was given large doses of vitamin C (3 gm. daily) and was told to drink an 8 oz. glass of citrus juice twice a day. After 2 months of this treatment, she stated that her menstrual periods had been shortened by one day, and that there was less bleeding than at any previous period in 19 years. She also stated that she felt better and "had more energy than ever." Her blood vitamin C level on starting the treatment was 0.9 mg. per 100 cc., and 2 months later it was 2.0 mg. per 100 cc.

Conclusion

Scurvy is a common condition even at the present writing, accounting for 5.45 per cent of the cases seen over the period of a year.[8]

In all cases of prolonged or abnormal menstrual bleeding of otherwise undetermined origin, consideration should be given to the possibility of scurvy as the basic cause.

Vitamin C can affect menstrual bleeding, even when the blood vitamin C level appears to be within normal limits (as in Case 3).

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7. Stander, H. J., Javert, C. T. and Kuder, K.: The management of abnormal vaginal bleeding. Surg., Gynec. & Obst. 75:759 (December) 1952.
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MEETINGS AND POSTGRADUATE COURSES

American Academy of Forensic Sciences: Sixth annual meeting, February 25-27, 1954, at the Drake Hotel, Chicago. Titles of all papers to be read must be submitted to Dr. Milton Helpern, program chairman, 106 East 85th Street, New York 28, by November 1, 1953.

University of Minnesota, Minneapolis: Continuation course in pediatrics for general physicians, January 7-9, 1954, at the Center for Continuation Study. Recent advances in the management of common pediatric problems will be stressed. Course is under the direction of Dr. Irvine McQuarrie, Professor and Head of the Department of Pediatrics.

University of Minnesota: Continuation course in obstetrics for general physicians, December 3-5, 1953, at the Center for Continuation Study. Emphasis will be on recent advances in the field which have practical clinical application. The course will be presented under the direction of Dr. John L. McKelvey, Professor and Head, Department of Obstetrics and Gynecology.

Emory University School of Medicine: Sixth annual postgraduate course for general practitioners, December 8-10, 1953. Program will include discussions on medicine, surgery, pediatrics, obstetrics and gynecology. Fee for the course is $15.00. Complete program available from Director of Postgraduate Education, Emory University School of Medicine, 69 Butler Street S.E., Atlanta 3, Georgia.

Postgraduate training program in obstetrics. Six month graduate training program in obstetrics offered at Grady Memorial Hospital in Atlanta. Program specifically designed for clinical training at graduate level in both normal and abnormal obstetrics. Full maintenance, including room, board and laundry service is furnished. No tuition charged. One graduate of an accredited medical school can be accepted for this program every two months.

Postgraduate course in electrocardiography, February 8-12, 1954, at Emory University. Course is designed for those with previous experience in electrocardiography. Fee for the course is $60.00.

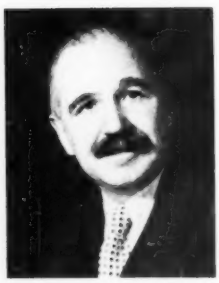
CASE REPORT

A New Approach to the Surgical Treatment of Rectal Procidentia

COLIN D. L. CROMAR

Ottawa, Ontario, Canada

Principles underlying operations used to correct rectal procidentia are reviewed. It is suggested that none of these procedures removes the factors primarily responsible for the condition nor do they prevent its recurrence. An operation is proposed and described which meets the necessary requirements—that the peristaltic wave in the colon be arrested before it reaches the rectum and that the rectum be formed into a pouch which can be emptied by anteroposterior compression. A case is reported in which the proposed procedure was successfully carried out.



COLIN CROMAR

RECTAL procidentia is a condition in which all the coats of a part or the whole of the rectum are everted and protruded through the anal orifice, the point of commencement of the eversion being at the mucocutaneous junction. It is to be differentiated from a protrusion of the mucous membrane only, a condition known as prolapsus mucosae recti or, sometimes, as prolapsus ani.

Many procedures have been advocated and practiced for the relief of rectal procidentia. It is not my intention to review these operations in an historical fashion but rather to indicate the principles on which they have been based. They fall naturally into four groups:

1. *Operations designed to overcome sphincteric atony by narrowing the anus*—These include such procedures as Duret's operation, König's sphincteroplasty, Lange's transverse rectorrhaphy, Thiersch's method of surrounding the anus with silver wire, linear cauterization, various forms of injection therapy, etc.

2. *Operations designed to resuspend the rectum and sigmoid colon*—Examples are Verneuil's or Lockhart-Mummery's operations, performed from below, and Jeannel's intra-abdominal colopexy.

3. *Operations consisting of excision of the prolapsed part of the intestine*—These vary from the simple method of strangulation of the prolapsed portion of the bowel between an encircling elastic ring and a hard rubber tube in the lumen, as practiced by Weinlechner, to the more extensive proctosigmoidectomy advocated by Mikulicz.

4. *Operations intended to create an extrarectal barrier to prevent rectal descent by obliteration of the pelvic cavity*—This type of operation was introduced by Moschcowitz and subsequently modified by Pemberton.

None of these operations has been entirely satisfactory. Those intended to narrow the anus have resulted all too frequently in impaired sphincteric control; recurrence has followed even the most elaborate forms of rectopexy; the amputative procedures added the risks of peritoneal contamination and stricture formation to that of recurrent prolapse and, although the results of the Mosch-

cowitz-Pemberton type of procedure have been more encouraging, the operation is technically difficult. The lateral folds of pelvic peritoneum are often inadequate to obliterate the pelvic gap, and both pelvic veins and ureters are liable to injury during the suturing process. But the main shortcoming of all these types of operation is that they do not deal directly with the cause of the protrusion and therefore fail to prevent the original etiologic factors from coming into play a second time.

To understand the cause of the protrusion it is convenient to study the horse, as this animal prolapses its rectum each time it empties its bowel. It does this because its rectum is a straight tube—in fact, it was the straightness of this tube in the lower animals that led the ancient anatomists to name it the intestinum rectum. During defecation, a peristaltic rush—a wave of relaxation followed by a wave of contraction—sweeps from the colon through the straight rectum and simply turns it inside out. The protrusion is rapidly reduced, partly by relaxation of the intestine and partly by the negative pressure which normally exists in the rectum of the erect, resting horse.

The healthy human rectum is not a straight tube but is thrown into transverse folds—the valves of Houston. Furthermore, the peristaltic rush in the colon stops short at the rectosigmoid and serves only to fill the rectum. Defecation takes place when a forcible contraction of the abdominal muscles diminishes the size of the abdominopelvic cavity and compresses the rectum, driving its contents through the anus in the direction of least resistance.

The essential difference is that the rectum of the horse is emptied by peristaltic pressure applied in the long axis of the bowel and acting like a piston in a syringe, whereas the human rectum is squeezed empty by anteroposterior compression like a tube of toothpaste.

The same difference exists between the patient with procidentia and the normal human being. In procidentia the valves of Houston are absent or poorly developed, the rectum forms a more or less straight continuation of the sigmoid colon and consequently is carried through the anus by the unbroken peristaltic rush. In contrast to the horse there is a slight positive pressure in the human rectum in the erect position which tends to aggravate the protrusion and to hinder its reduction.

For the surgical correction of procidentia therefore, two principles emerge: (1) to arrest the peristaltic rush at the level of the rectosigmoid; (2) to convert the rectum into a passive pouch which can be emptied by anteroposterior compression. Both these aims can be accomplished by deliberate plication of the rectum.

Surgical Procedure

The rectum is exposed through a low midline incision. The lateral folds of peritoneum are divided along with that forming the rectovesical pouch. The rectum is mobilized from the hollow of the sacrum by blunt dissection, as in an abdominoperineal resection. It is then arranged in folds, like the coils of a radiator, and these are held in approximation by nonabsorbable sutures. The peristaltic wave is thus arrested and pressure on the rectum tends to compress the folds against one another.

Case Report

A 70 year old white male with procidentia was referred to me by a local physician on January 28, 1952. Fifteen years previously the patient had consulted a proctologist about the same complaint, which had then existed for about 9 to 10 months. A perineal sphincteroplasty performed at that time resulted in complete loss of anal sensation and sphincteric control. A few months later he had an abdominal rectopexy performed by another surgeon. After this he still had a protrusion at the anus whenever he stood up or strained. He could keep it in place when he concentrated on it but any unguarded movement would bring it down. He experienced constant seepage of mucous and had to wear a pad all the time. He kept his bowels regular with laxatives and an occasional suppository. His appetite was good and his weight was well maintained.

Rectal procidentia *(right)*. Drawings illustrate the surgical procedure discussed in the text.

His family and marital histories were noncontributory. In 1913 he had been under observation for possible tuberculosis. Forty-five years ago he had been incapacitated for three months by a crushing injury of the spine. About 20 years ago he had had surgical repair of bilateral inguinal hernias. His prostate was resected eight years ago.

The patient told me that he had stopped playing tennis and badminton only during the past three or four years. Results of the physical examination were normal. The anus was lax and insensitive and the perianal tissue tended to bulge. There was some degree of sphincteric control, but when the patient strained there was a procidentia of the lower rectum for a distance of 3 or 4 inches. The surface of the bowel was healthy and with the patient lying on his side, the extruded portion returned spontaneously into the rectum when the straining ceased. Digital examination showed a lack of support of the lower rectum. The prostate was enlarged to about three times its normal size.

Operation—On April 2, 1952, with the patient under general anesthesia, the abdomen was opened through a low midline incision. There was no evidence of the previous rectopexy. The rectum was straight and a deep peritoneal pouch existed in the rectovesical space. The lateral reflections of the peritoneum were divided with scissors on either side of the lower sigmoid and rectum and the incisions were carried forward across the rectovesical fold. The rectum was then stripped up gently with a hand in the hollow of the sacrum. It was found possible to arrange the rectum and lower sigmoid in four transverse folds, each measuring about 2½ to 3 inches in length. The adjacent loops were sutured

to one another, using interrupted sutures of black silk. The peritoneum was united in front of the plicated rectum and was reinforced with a strip of prepared ox fascia. The appendix was removed prophylactically and the abdomen was closed in layers without drainage. The patient was then turned on his right side and ligatures of heavy braided silk were applied to three points on the circumference of the anal mucosa and in the left lateral, right anterior and right posterior anal quadrants, in an attempt to narrow the patulous anus slightly without further damage to the sphincteric mechanism.

The patient made an uneventful recovery and left the hospital on the fourteenth postoperative day.

A barium enema was administered on April 15 and was reported as follows by Dr. R. J. Patterson, Department of Radiology, Ottawa Civic Hospital: "Some infolding of each side of the rectum is noted just distal to the rectosigmoid junction and slight irregularity is noted along the left side about an inch and a half from the anal sphincter. These deformities may be the result of the plication. Otherwise nothing abnormal is seen."

After the patient's visits to the office the following notes were made:

April 25, 1952—Abdominal wound well healed. Anus contracts well but he does not have full control. No prolapse on straining.

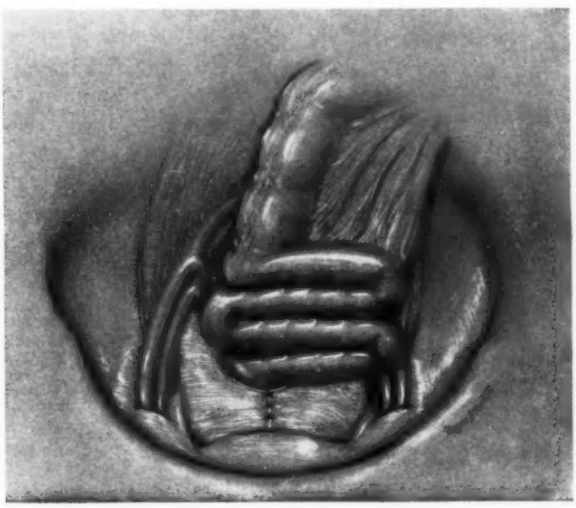
May 2, 1952—Rectum is staying up. Control of sphincters is good but anal sensation is lacking because of previously paralyzed nerves.

May 9, 1952—No prolapse. Patient says he feels as though there were a "bar" inside the rectum which prevents it from coming down. Control is improving steadily.

August 11, 1952—Patient has good control except for liquid feces. Rectum well supported. Wears pad and has to take laxatives but is comfortable.

The immediate result of this operation was therefore very satisfactory, any impairment of control being due to damage to the sensory nerve supply at the anus from a previous operation.

August 31, 1953—Patient now has almost complete control, although sensation is lacking. He has to take laxatives regularly to make his bowels move. There has been no recurrence of prolapse. As a protection against leakage of fluid stools he wears a pad constantly. However, he states that whereas a box of these pads used to last him only 28 days, he now need buy a box but once in three months. He is completely satisfied with the result of the operation.



Comment

A surgical procedure can be successful only if it is based on sound physiologic principles and, in the final analysis, it is to be judged only by the end result. Interference with the sphincteric apparatus by attempts at sphincteroplasty does not deal with the underlying cause of the protrusion and can, at best, only create a rather unphysiologic barrier to obstruct the descent of the rectum.

Where sphincter atony exists it is secondary to the dilating effect of the procidentia and can probably best be dealt with by the Salmon ligature method, which causes anal contraction by mucosal puckering only, without injuring the sphincter muscles. The suspension operations have usually proved to be unable to stand the shearing strain of the peristaltic rush in the intestine. They have little anatomic or physiologic justification, for examination of the normal rectum will reveal that there is no particularly elaborate system of suspension present to keep it in place. Similarly, the amputative operations have failed to remove the forces responsible for the procidentia. After the protruding part has been removed, protrusion of the proximal bowel may occur and cases have been reported where the entire colon—and even part of the ileum—has prolapsed through the anus. The Moschcowitz-Pemberton operation stresses the importance of the peritoneal sac in the rectovesical pouch and an analogy is drawn between this and the sac of the ordinary "sliding" hernia. However, it seems likely that the sac is a secondary traction effect caused by the eversion of the rectum. It is possible that the success reported after some of these procedures was due more to the fact that a fold was created in the rectum than to the attempt to obliterate the cavity of the true pelvis.

The essential requirements for the surgical cure of procidentia would appear to be to arrest the peristaltic rush in the colon before it reaches the rectum, and to form a terminal pouch which can be emptied by anteroposterior compression. Both these requirements would seem to be met by the procedure of plicating the rectum and lower sigmoid and thus creating artificial valves of Houston as outlined in this report. In my experience, rectal procidentia has been a rare condition, even in the hospitals devoted to diseases of the rectum. Few cases are encountered by the individual surgeon. This report is submitted, therefore, in the hope that others will see fit to try the procedure or, at least, the principles embodied in it and to make their results public, so that it may receive a fair trial and its value may be truthfully assessed.

CASE REPORT

Triple Primary Carcinoma

JAMES T. LACEY*

Harrington Memorial Hospital, Southbridge, Massachusetts

The rarity of triple primary carcinoma is emphasized in the presentation of this case report. It is believed that the findings adhere strictly to the criteria laid down by Warren and Gates. The length of time which elapsed between the two hospitalizations for cancer of the breast—19 years—is of interest.

A REVIEW of the literature on the subject of multiple cancer reveals that the number of reports is not plentiful. Barrett, et al.[1] found the reported incidence of multiple primary malignant tumors (from 14 sources) to range from 0.3 to 6.8 per cent. They also found that the average interval between occurrence of cancer in such cases was 3.22 years, the longest being 14 years.

Block and Hone[2] reported a case in which four carcinomas were found at different times (both breasts, uterus and colon). They stated that these were primary malignancies with no real evidence of recurrence, and although the malignant lesions were of different grade, all were adenocarcinoma.

Morrangoni and McKenza,[3] in 618 cases of carcinoma of the female genitals, found 15 cases of multiple primary cancer; of these 15, 2 were triple primaries (breast, sigmoid and uterus; uterus, ovary and colon). Bugher[4] stated that the probability of a female patient with carcinoma having three primary carcinomas is 0.34 per cent.

Warren and Gates[5] liberalized the criteria for differentiating primary malignant disease (proposed by Billroth and later revised by Goetze):

1. Each tumor must present a definite picture of malignancy.
2. Each tumor must be distinct.
3. The probability of one tumor being a metastasis of another must be excluded.

The following case report presents the development of three primary carcinomas during a period of 19 years. All three carcinomas adhere to the criteria laid down by Warren and Gates.

Report of Case

A 41 year old white woman of French extraction was admitted to the Harrington Memorial Hospital on September 8, 1932, complaining of a lump in the right breast. The tumor had been noted for five weeks. There was occasional pain in the tumor. There was no history of trauma. The patient was married and the mother of four children. There was no family history of carcinoma, but her father had died of "prostatic disease."

Physical examination was entirely negative except for the palpation of a small, hard mass in the middle of the upper half of the right breast. The mass was movable and not attached to the skin. A diagnosis of cyst of the breast was made.

The tumor was excised under local anesthesia and the patient was discharged.

*Visiting Surgeon, Harrington Memorial Hospital, Southbridge, Massachusetts.

Pathologic report—Gross—An opened cyst measuring 2 by 1.5 cm. with a wall 0.5 cm. thick, surrounded by fat. Microscopic—Proliferation of epithelial cells attempting gland formation. Mitosis present. Diagnosis: adenocarcinoma of breast, high malignancy.

The patient was readmitted to the hospital on October 3, and a radical amputation of the right breast was performed.

Pathologic report of resected specimen—Gross—Several glands about the size of a pea; a breast with pectoral muscles. No nodules found in the breast tissue. Microscopic—Axillary glands show no metastasis; a section of the breast shows papillary growth of epithelium into small cysts. It does not appear to be malignant. Diagnosis: papillary intracystic adenoma and chronic lymphadenitis.

The patient's convalescence was uneventful, and she remained well for the next 10 years, during which time her course was followed closely. There was no evidence of metastasis. The patient had no x-ray therapy.

The patient was next admitted to the hospital on January 25, 1951, at which time she was 60 years old. Two months previously she had noticed a lump in her left breast; some pain had also been present.

Physical examination disclosed thé absence of the right breast. There was no evidence of local or distant metastasis. An x-ray of the chest showed no metastasis. In the left breast was a hard mass about the size of a lime just under the nipple and not attached to the skin or nipple. The nipple was retracted. The rest of the examination was negative.

A diagnosis of carcinoma of the left breast was made, and an operation performed the following day. Frozen section revealed carcinoma, and a radical amputation was done. Convalescence was uneventful.

Pathologic report of resected specimen—A mass of breast tissue and fat measuring 7 by 7 by 3.5 cm. The nipple, which is inverted, is included in the skin on the surface which measures 7 by 3 cm. The specimen contains a very firm tumor measuring 3 by 2 by 2 cm. The mass is not encapsulated and is adherent to the surrounding fat. The pectoral muscles and a piece of fat tissue are also included. On section, the muscles and fat tissue are negative. The axillary contents contain four glands averaging 5 mm. in diameter and imbedded in fat tissue. Microscopic diagnosis: breast tumor—medullary carcinoma; axillary glands—chronic lymphadenitis; no metastasis found.

Two months later, on March 10, 1951, the patient was again admitted to the hospital, this time with a diagnosis of intestinal obstruction. The chief complaints were pain in the abdomen, nausea and constipation. Her history included an appendectomy 30 years previously, carcinoma of the right breast 19 years previously and carcinoma of the left breast two months previously. Four days before this third admission, she began to have a swelling of the abdomen and pain in the right lower quadrant associated with nausea and increasing constipation.

Physical examination disclosed the absence of both breasts. There was moderate distention of the abdomen, and a slight fluid wave was present. There was tenderness in the right lower quadrant and above the pubis. On pelvic examination, there was a hard mass involving the area of the uterus. Rectal examination revealed the same hard mass, apparently attached to the posterior surface of the uterus.

X-ray examination of the chest showed some degree of tenting of the right diaphragm of no significance. A flat plate revealed a calcified gallstone. The results of a barium enema were reported as follows: "The colon filled with difficulty. There was a persistent narrowing in the sigmoid colon. The bowel above this was narrow and did not empty well. The liver appeared enlarged with a depression of the hepatic flexure downward. Changes are most probably due to malignancy." A diagnosis of partial intestinal obstruction was made and the patient underwent operation on the third hospital day. A large amount of clear fluid was found in the peritoneal cavity. Both ovaries were frozen behind the uterus in the cul-de-sac. There was extensive metastasis to the peritoneum, bladder and omentum, but not to the liver. One gallstone was found in the gallbladder. Biopsy specimens were taken

from both ovaries and from the omentum, and the abdomen was closed.

Postoperatively the patient ran a slight fever—99 to 100° F.—which persisted throughout her hospital stay. She also had intermittent vomiting and anorexia. Intravenous fluids were given daily, and the patient was discharged on the ninth postoperative day in fair condition.

Pathologic report of biopsy specimens—Gross—Specimen consists of 11 pieces of white, moderately firm tissue varying in size from 0.4 cm. in diameter to 2 by 1 by 0.7 cm. Microscopic—Biopsy of ovary, papillary carcinoma, grade 3. Biopsy of omentum, metastatic carcinoma. Comment: This does not appear to be metastatic from the breast carcinoma.

The patient's progress at home gradually worsened, and she died three months after her last operation of metastatic carcinoma of the ovary.

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CHOICE OF OPERATIONS FOR DUODENAL ULCER

THE gastric hypersecretion that causes duodenal ulcer is dependent on two factors: (1) vagal stimulation from higher centers and (2) hormonal stimulation from the mucosa of the antrum. Operations for duodenal ulcer are based on control of one, the other, or both of these stimulatory mechanisms.

The conventional surgical attack, partial gastrectomy, is not a satisfactory answer to the problem of duodenal ulcer. Although resection of the antrum removes one of the factors that causes hypersecretion of acid, the remnant of the fundus remains connected to the central nervous system by the vagus nerves, and hypersecretion frequently continues. This results in a high incidence of recurrent ulceration unless 70 per cent or more of the stomach is removed.

In extensive resections of over 70 per cent of the stomach, sound physiologic principles have been abandoned, and the surgeon resorts to mere removal of the major part of an important and undiseased organ. Unfortunately these radical gastrectomies are often followed by side effects just as incapacitating as the original ulcer.

Vagotomy has not given any better answer to the problem of duodenal ulcer than has partial resection, because in vagotomy the stimulatory mechanism of the antrum is not removed and the incidence of recurrent ulceration is unacceptably high. Gastric retention, moreover, frequently occurs, unless a drainage operation, such as gastroenterostomy, is simultaneously performed.

Vagotomy with gastroenterostomy has been utilized extensively as a substitute for gastric resection, but here again the results are far from perfect. The original report of the National Committee on Peptic Ulcer published in the November 1952 issue of *Gastroenterology* indicated that gastric resection was attended by better results than vagotomy and gastroenterostomy. But a revised report, published in the June 1953 issue of the same journal, admitted that a transposition of figures had occurred and concluded that there was no statistical difference between the results of the two operations unless, in the resected cases, over 70 per cent of the stomach were removed. Since it is not always technically easy to remove over 70 per cent of the stomach, this is like saying that gastric resection is the best operation when it is technically easy to do it or, conversely, that vagotomy is the best operation when it is complete. The fact remains that, despite the arbitrary nature of the Committee's criteria of evaluating results, there was no statistical difference between the results of gastric resection and of vagotomy with gastroenterostomy. The Committee's criteria, moreover, take no account of the relatively high mortality of radical subtotal resection, of the nutritional disturbances that frequently follow it, and of the high incidence of the dumping syndrome

that occurs when most of the stomach is removed.

Although the mortality rate of vagotomy and gastroenterostomy, in experienced hands, need not be over 0.5 per cent, and although the side effects are minimal if the gastroenterostomy is properly placed, clinical evidence of recurrent ulceration in a careful 5 year follow-up will be approximately the same as that following a conventional two-thirds gastrectomy, between 5 and 8 per cent. In order to avoid this high recurrence rate and at the same time to avoid the morbidity of radical gastrectomy, Johnson and Orr of London have performed vagotomy associated with a two-thirds gastric resection in 236 patients, and have employed vagotomy and gastroenterostomy when the risk of resection seemed too high. In gastric ulcer, when the factor of hypersecretion did not play a part, they removed two-thirds of the stomach without resection of the vagi.

The mortality rate in Johnson and Orr's "policy group" (i.e., the group in which they did the operation best suited to the individual case) was only 1.1 per cent, as compared to a 4 per cent mortality in radical resections. The results were highly satisfactory, no recurrences of ulceration having taken place in the 5 year period studied. The "policy group" also showed a lower incidence of every side effect and a higher proportion of satisfactory results.

Although in the beginning of the controversy there were strong prejudices in some quarters against vagotomy and, in others, against resection, more and more surgeons now realize that the compromise operation, vagotomy with resection of the antrum, is based on sound physiologic principles. It is now apparent that the combination of these two physiologic methods controls the ulcer diathesis more completely than even a very radical gastrectomy and does so with less risk and with fewer side effects. When this operation can be employed safely, it approaches the ideal treatment of duodenal ulcer. When increased risk is involved, vagotomy with gastroenterostomy gives safe and satisfactory results.

GEORGE CRILE, JR.

WORLD DIRECTORY OF MEDICAL SCHOOLS

For years various agencies have contemplated the publication of a world directory of medical schools. The World Health Organization, however, has finally completed this project and has just published such a directory. The information was obtained by sending questionnaires directly to the institutions themselves. When replies were not forthcoming, information was sought from other available sources. *The Journal of the American Medical Association* and the "American Medical Directory" made available full information concerning the medical schools of the United States and Canada. A survey of the new publication indicates that a very small amount of the information it contains is already obsolete, but the directory does supply full information concerning more than 500 schools and this is exceedingly useful.

The "World Directory of Medical Schools" is published in two languages—English and French. The data are arranged alphabetically by countries and within countries by cities. Where there is more than one school in a city, as for example in such centers as Chicago, New York and London, the schools are arranged in alphabetical order. There are at this time 12 medical schools in London and many great capitals have 4 or 5 medical schools.

The information concerning the individual medical schools is arranged in 13 columns which supply the name of the school in the national language, the year founded, the administration, the academic year, the conditions for admission, the number of teaching personnel, the total enrollment including male and female, the number of new students admitted annually, the language used for instruction, the duration of study, the degrees awarded, and the annual number of graduates, ending with the annual tuition fees as quoted in local currency. Unfortunately, 20 pages near the end of the book contain only the column headings since the Union of Soviet Socialist Republics did not answer any questionnaires and the information was not ob-

tainable in any other manner. Apparently the rest of the world cooperated.

The World Health Organization is to be congratulated on this masterly achievement. Copies of the directory are being sent at once to the deans of the various medical schools together with a suitable blank so that all of the information may be brought up-to-date for the second edition. Copies of the book may be obtained from the World Health Organization either by writing to its headquarters in Geneva or to its branch offices throughout the world.

MORRIS FISHBEIN

HAZARDS OF LOW VOLTAGE IN INDUSTRY

AMONG the greatest of hazards in industry are those associated with the use of the potent force called electricity. C. C. Haggard, Safety Director, California-Oregon Power Co. of Medford, Oregon, has just called attention in "Occupational Hazards" to the dangers associated with the use of low voltage hand tools.* These are found not only in industry but perhaps even more often and more hazardous in the little basement workshops all over the country in which men find recreation and a useful hobby.

Electric shock may cause death by paralysis of the phrenic nerves, by the searing and burning of important organs and tissues and by direct disordering of the mechanism of the heart. Obviously, paralysis of the phrenic nerves stops respiration; in such cases, artificial respiration promptly applied may restore breathing. Thermal damage comes mostly from high voltage shocks but may occur also with low voltage; when tissues have been burned, scientific treatment is necessary. When the heart stops because of fibrillation from overstimulation by electric current, the normal rhythm may be restored by actual manual massage of the heart after the opening of the chest. In all instances, artificial respiration, promptly and scientifically applied, may make the difference between life and death.

Much depends on the type of current, the voltage, the resistance of the body, the path of the current through the body, the amount of the current and the length of time the body stays in contact with the current.

Mr. Haggard finds that the maximum amount of alternating current electricity that man can take without injury is probably only one milliampere. Five milliamperes is the maximum charge allowed in electric fences. You may be able to let go of a wire carrying five milliamperes charge. The average person will be frozen to a charged object carrying 12.4 milliamperes, and if the hands are wet this requires less than 20 volts. Electricians who are properly trained approach charged objects with the back of the hands to avoid freezing the palm to a live wire.

Physicians frequently find that they too are exposed to hazards from contact with electricity, particularly those who work in roentgenology and physical medicine. The recent action of leading bodies in the electric and medical fields in approving the Holger-Neilsen technic for artificial respiration suggests that everyone who is exposed to the hazards of electricity learn this technic at the earliest possible moment, teach it to his associates and be prepared to use it when an emergency arises.

MORRIS FISHBEIN

*Low Voltage Can Kill! Occupational Hazards, July 1953, p. 21.

PATIENTS' ATTITUDES TOWARD FEES

FROM the Wayne County Mental Health Clinic in Detroit comes a report indicating that what a patient does about fees may be taken as evidence of his mental attitudes and resistances. Exploration of this behavior of patients can be utilized for interpretations in terms that are important to the patient.

Some patients may feel that they must pay for their treatments well in advance. According to Dr. Louis Koren and Dr. James Joyce,* this type of behavior usually represents an attempt to placate or bribe the therapist. The

*KOREN, LOUIS and JOYCE, JAMES, M. A.: The treatment implications of payment of fees in a clinic setting. Am. J. Orthopsychiat. 23:350-357 (April) 1953.

patient, they say, projects his own aggressive impulses on the therapists and fears retaliation. In some instances in which patients attempt to pay high fees out of proportion to their incomes, the patient has intense feelings of guilt and wishes to control the relationship. When the patient insists on a disproportionately low fee, this may be taken as a desire on his part to relegate the doctor to an inferior status.

Continuing this interesting discussion, the investigators find that the patient who withholds information regarding his financial status and pays a fee that is not commensurate with his economic position is using money in an irrational way. Such patients apparently hold onto money partly as security and partly because they get some erotic gratification by holding onto the money and then offering it as a gift to the doctor. Some patients express hostility toward the doctor by the manner in which they pay the fee. They may insist on paying in small coins or in driblets or with a residue always remaining, or indeed they may forget altogether to make payment.

Money is an important part of our culture. The psychoanalysts usually equate attitude toward money with attitude toward feces. The patient's irrational attitude toward money may therefore be historically determined in relationship to his childhood and can indeed reflect his progress and motivations. However, the disinclination of a considerable portion of the public to paying medical bills does not somehow seem to be in exact ratio to the widespread use of cathartics and laxatives.

MORRIS FISHBEIN

DANDRUFF AND PITYROSPORUM OVALE

For some years, advertising announcements in many periodicals which accepted the advertisements emphasized that a certain proprietary antiseptic, which seems to be essentially liquor antisepticus, could eliminate from the hair and the hair roots an organism called *Pityrosporum ovale;* this, the advertisements insisted, was the cause of dandruff and other seborrheic conditions of the scalp. Now a definitive research has been made in Great Britain which included the examination of 200 normal scalps in an attempt to correlate the degree of infection with *P. ovale* and the extent of dandruff.[1] The investigators have concluded that there is no evidence to justify the theory that *P. ovale* causes dandruff. Instead the degree of infection is influenced by the quantity of sebaceous secretion. The increased flow of sebum at puberty is sufficient to explain the rise in the incidence of dandruff at that age. Dandruff was heavier in women than in men.

At the same time, the suggestion that estrogen will diminish the degree of dandruff and the extent of infection with *P. ovale* was not supported by the results of the examinations of 100 men and 100 women, including scrapings from the scalp. The investigators concluded that *P. ovale* is not the cause of dandruff, and that it is instead a harmless organism on the scalp which thrives best in a medium provided by a heavy flow of sebum.

In 48 men and 33 women there was an absence of dandruff even in the presence of heavy infection with *P. ovale.* The British investigators conclude that dandruff is simply normal desquamation of the scalp, similar in every respect to the invisible scaling on other parts of the skin. The difference lies in the fact that the hair of the scalp holds the scales. The authors are inclined to admit that the internal secretions, including particularly the sex hormones, are in some way related to the growth of hair and to the extent of the secretion of sebum but they cannot feel that these conditions can be controlled by use of added sex hormones.

MORRIS FISHBEIN

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The Therapeutic Art

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An analysis of medical motivations and directions is attempted because the combination of these known and unknown factors constitutes the therapeutic art. Distinction is made between (1) the scientific therapeutic indication based on logic but often leading to too mechanical thinking, (2) the suggestive indication influenced by the emotional needs of the patient and his environment and (3) the subjective indication based on subjective needs and motivations of the therapist.

THE art of therapy involves more than applied scientific deduction. That is why I will try in this essay to analyze some objective and subjective motivations that influence the medical art.

A deplorable difference exists between the physician who cures and the scientist who makes a diagnosis only. When the acute emergency of a disease forces immediate intervention, the diagnostic intellect hesitates while the therapeutic and helping instinct often acts even before thinking.

The medical student is aware that he is chiefly taught extensive diagnostic knowledge, but he is not given much instruction about the art of therapy. He must teach himself that therapeutic ability later. A synthetic science of the therapeutic arts does not even exist at present; pharmacology, immunology and surgery are only specific physical and chemical introductions to such sciences of therapy. Systematic psychotherapy is just in its beginning. Because we still lack a general science of therapy, medical science is burdened with a tragic conflict that may lead to therapeutic nihilism. This is certainly not the aim of medicine. Many a young physician, as well as the public, speaks with disdain of ampules, powders, pills, lotions and ointments. He is derogatory of operations or analytic treatments. The public, with its naive criticism or affirmation of various kinds of therapy, forces many doctors to act according to its wishes. The drug manufacturer often tries to suggest to the physician what his future therapeutic action should be. This strategy is often more pronounced in the nonofficial and pseudomedical schools and among quacks and shamans who utilize our lack of systematic study of therapeutic methods to introduce their magic skills. Much of the therapeutic reaction will depend on the subjective attitude of the doctor toward his patient and on the latter's need for intervention, thus forcing the doctor to follow certain lines of therapy. Modern psychology knows more about this mutual relationship between doctor and patient. Many patients get better only because they wish to please their physicians or because their physicians please their neurotic needs.

When the physician asks himself if it is time to act, to do something in addition to the *vis medicatrix naturae*—the natural curative forces—he studies pathologic symptoms and other indications that will determine

therapy. Nature has presented the symptoms of illness; now comes the therapist to alleviate the illness. The physician places *skill* and *science* in opposition to the processes of disease.

Bleuler[1] in his book on medical thinking asks if this kind of immediate therapeutic thinking is right. The physician's question implies that he wants to give treatment per se without asking himself if such intervention is really needed. Almost no physician exercises *udenotherapy* or gives placebos on behalf of conscious medical abstention. Most patients would not allow it. Our therapeutic activities even make real knowledge of disease more and more difficult, because in actual life we now rarely encounter untreated symptoms.

The medical school teaches many definite indications of specific treatments. Not being mature in his medical thinking, the student must follow these teachings or risk error. This educational suggestion gives the idea of a stable form of pathology that does not agree with the ever changing picture of reality.

Is the definitive therapeutic indication wrong? No, we need this form of well defined medical prescription in emergency cases, but the belief is wrong that only one way of action is good in each case. However, with our science of therapy just beginning, we must not expect to learn an unambiguous therapeutic truth—an impossibility in a science of life.

What does therapy mean? The therapist looks for a certain directive plasticity in life that will offer a basis for change in the sick process of the human being, so that the therapist may be able to lead the pathologic development into new and healthier ways of life. This can be done in one of two ways. The morbid influences—noxious facts—can be eliminated or neutralized; we may speak in this way of an antinoxious therapy or antitherapy. But the other way is also possible; to correct and stimulate the living autarky of our psychosomatic structure, e.g., to stimulate the inner curative processes and defenses. I propose to speak in this case of a constitutional therapy or protherapy. In daily medical actions, we always find a combination of both principles.

Sometimes the school may teach treatments which fail completely in practice. At other times, there are confusing differences of opinion. That the student wants well defined indications and directions is good, for without them he would be confused and hesitant in the midst of manifold opinions.

There is only one person to whom this therapeutic dilemma does not matter—the patient himself. He does not belong to any diagnostic school nor does he prefer any therapeutic rule. He is just a human being who lives once and uniquely in spite of all scientific ruling. He wants to be helped; that is all!

Every therapeutic decision is essentially an opinion of one individual about another. The doctor decides with his acquired sets of opinions and prejudices and the patient reacts with his preconceived expectations and needs.

How is the sharp scientific therapeutic directive born? Whenever the rationale of our treatment is at stake, we cannot escape some thinking about the methods we use.[2] I propose to make a division into scientific, suggestive and subjective directives. The *scientific indication* is generally accepted; it is the result of analysis of many facts, so that its logical conclusions cannot be denied. The *suggestive* indication comes from the picture presented by the patient—his attitude, a certain striking symptom, or his subjective needs which force the doctor into a certain therapeutic act. The suggestive indication is dependent upon the patient or his environment, his cults and sophistications. The *subjective* indication comes from the doctor: his personal attitudes, his conscious and unconscious motives decide his form of therapy.

1. THE SCIENTIFIC INDICATION	Experimental indication Statistical indication Historical indication
2. THE SUGGESTIVE INDICATION	*Indicatio vitalis* Social indication Monosymptomatic indication
3. THE SUBJECTIVE INDICATION	Transference and countertransference *Indicatio "utque fiat"* *Indicatio "pro domo"*

The Experimental Indication

This program of scientific action is a result of that part of the medical science that at present is held in most esteem. The scientist asks Nature a question by means of experiment and uses the answer to determine further action. An example of such experimental indication is the treatment of serum allergy. If it becomes necessary to inject therapeutic serum, after having formerly used serum from the same animal on the patient, it may be expected that the patient has become allergic. Instead of one direct shot, the fractioned dosage of Besredka may be used. This method results from answers to questions concerning therapy the scientist has asked of Nature, i.e., the guinea pig. The experiences from animal experiment are thus transferred to clinical use for man.

This method assumes that Nature is able to give a single answer to a question. Medical theoretical thought is guided chiefly by generalized causal thinking—that every special case is part of a generally valid law. In practice, however, experience proves that there are no simple generalizations in therapy. We always find changed circumstances because of certain individual and constitutional factors. As an example, although we are familiar with the soporific action of barbituric acid, in some patients with brain disease these drugs act paradoxically and cause excitement instead of sleep.[3] The difficulty in therapy is to compromise between known general biologic reactions and the unique individual constellation and reaction. Every therapy moves between generalization and individualization.

The Statistical Indication

From a variety and multitude of former experiences, we wish to establish a therapeutic directive for the future. A majority of useful therapeutic experiences establishes the expectation that we will meet with the same success in succeeding cases. That is why the scientific critic always asks for large statistical figures when evaluating therapeutic success. We may call this the dictatorship of numbers. However, when one studies the history of medicine, and the reports of impressive results in large numbers of patients with medicaments that are now obsolete, one concludes that something is wrong with our comfortable statistics. Nothing has changed as much through the ages as therapeutic success; after great success, the new cure disappears into oblivion.

In the first place one often forgets that psychosomatic man and his changing and growing structure cannot always be utilized in statistics. It may be that within a few years his pattern of reactions will have changed completely. Collective changes and expectations will play a role in this. For example, after a cerebral accident, man's pharmacologic sensitivity and toxic vulnerability will have changed.[4] Furthermore, not enough attention is given to the fact that in biology one well studied case sometimes can teach us more than many therapeutic successes studied more superficially. Each case is a meeting point and cross section of manifold general laws.

Besides this, how difficult it is to interpret statistics! And how easy to give them a favorable aspect! How many statistical figures are launched to serve the honor or prestige of a certain clinic! There even exists a special technic to "correct" therapeutic statistics and to eliminate the bad factors.

Every newly discovered medicament means a revolution in therapeutic habit formation. In the beginning the new drug cannot do much better than the older ones because we have no statistical comparisons. I do not speak about those fascinating discoveries proving immediate new results (antibiotics, ACTH). But here, too, there is the tendency to generalize their use as an arcanum and we lose statistical and therapeutic insight. Another determining factor in statistical results is the group of patients who provide the material for the study. Most definitive therapeutic indications come from medical schools and university hospitals. But in those clinics a special social group of patients is chiefly treated. In Western Europe there is even more difference. Usually, only the poor visit the university hospitals. Many physicians have found again and again that the "golden" private practice has

a different basis for psychosomatic reactions. The sensibility and vulnerability of a well trained laborer are different from those of an old, inbred family. That is important in surgery. We find in biology that in a too differentiated and refined organism there is less ability for regeneration. Surgical success, after all, is the result of spontaneous regeneration of the organism, besides the well applied technical skill of the surgeon.

From the clinic we want statistics of facts, the social reaction of the patient and the mind of the scientist who observes. However, at the same time we want observation of single cases, for they teach us the variability of the reaction of life. Let us look at a few examples:

Modern surgery of the sympathetic nervous system teaches us to heal with success some forms of intolerable pain. This kind of therapy will be more difficult to apply when the mental reactions in patients are more subtle and complicated. As soon as the pain means neurotic conversion, surgery, however suggestive it may be in the beginning, only helps temporarily. These forms of continual pain may be treated better with psychotherapy. There may be some pain, brief but so intense that it becomes a new, morbid emotion for the patient. I once treated a patient with trigeminal neuralgia, who never overcame the painful trauma of the now old-fashioned alcohol injection of the gasserian ganglion. The injury of the operation seemed to be more catastrophic to him than the old neuralgia.

Eugenics is a part of medical science which tries to prove, with figures, the usefulness of certain preventive measures. For example, it wishes to prevent the procreation of inferior genes by sterilization of human beings. I have two criticisms in relation to the mechanical side of this argument. First, the young science of genetics has until now only been observed for three generations of human beings in order to come to a certain conclusion. That is not enough for the discovery of valuable genetic rules in man. But there may be something that evades the tentative rule of genetic science, and that is the spontaneous and unique biologic development. One usually studies what can be causally and statistically interpreted and only that part can be suppressed by means of sterilization.

The Historical Indication

This therapeutic directive is the beloved child of old clinicians. When the experiment cannot direct or prove our way of action and when even the statistics cannot give any positive suggestion, then most clinicians revert to the revelation of old clinical bedside experience. There is something of a mystic trust in historical facts and a magic aura around old medical prescriptions.

The historical outlook always gives a long section of medical experience! Because their own era is too confused, many seek further truth in past experience. It is true that in medical practice clinical experience with drugs has taken place mostly before pharmacology was able to give reasonable explanations for its therapeutic results. That is why historical study is still able to offer many new approaches to therapeutic problems. There are many examples of this: Quinine, arsenic and mercury came to our medical arsenal long ago. We find many other old medicaments whose exact pharmacologic actions are still obscure, such as Kal. jodetum, arsenic, strychnine, salicyl, etc. Gradually, however, the newer pharmacology gains ground and will be more able to direct the uses of drugs.

The Social Indication

Man is simultaneously an individual and a member of a group or community. To cure a human being means not only to help him in the struggle against natural disastrous forces but also to fit him for certain social tasks and adjustments. Man, the individual and the member of a social organism, needs the help of that organism, as a plant needs its roots.

Disease is never a purely biologic reaction; it is also a failure to adjust to social life, and is always associated with the struggle for life. Because of the difficult struggle for life, the physician often must choose a form of therapy that considers the special social and economic situation of the patient.

Especially in psychiatric diseases do we need this social approach. The mentally ill

person is known as someone who is harmful either to society or to himself. He suffers from inner or outer forces, dependent, of course, upon the mental and social habits in his group.

In modern therapy more attention is given to the social validity and adjustment of patients. Modern therapy of fractures is directed to obtain restoration of function as soon as possible, in opposition to the old surgical therapy which gave more attention to anatomic repair. Some forms of treatment of tuberculosis, for example, artificial pneumothorax and thoracoplasty, are usually done in relation to the functional cure and mental activity of patient, contrary to the long rest cure in a sanatorium. Modern drug therapy again has changed this therapeutic behavior; extended treatment in a hospital or a sanatorium may make an unsociable being of the patient.

The different social security laws have effected a change in medical motives. In some cases the physician must be a kind of detective in order to be able to select the imagined complaints from the real symptoms of disease. Instead of diseases he has to treat the wish to be sick or the wish to escape into the protective disease. My experience is that this psychologic knowledge leads too much to a certain suspicious approach on the part of the doctor toward the social security patients. Real simulation of disease after an accident is seldom seen. In the army, many a physician tended to develop the same aggressive, suspicious attitude toward victims of battle neurosis. Every doctor is unconsciously afraid of his own infantile wishes, and this makes it difficult for him to evaluate neurotic symptoms objectively.

The Vital Indication

The emergency signal sounds! When the signs of death threaten, every therapist hesitates a moment. No matter how scientifically we can influence a biologic occurrence, we cannot conquer eventual death. When an emergency forces us to act to prevent impending death, we want a clear indication how to act, how to lengthen life, before using more complicated methods. Such is the doctor's religion, his belief in the sacredness of life itself.

In acute lethal danger nearly all therapy becomes rather simple. It is as if, in the moment of danger, clashing medical opinions meet. We apply cardiotonics, transfusions, tracheotomy, etc. before the more causal therapy is used, because life must not escape us. *Ars longa, vita brevis*, Hippocrates taught us, and the good moment passes soon.

In acute danger every doctor is glad to have a clear pattern of action; the therapeutic activity helps him to conquer the general human fear of death. In this area the competition with quacks and mystic therapy suddenly disappears.

The Symptomatic Indication

All kinds of primitive and archaic opinions still live in the midst of scientific medical thought and they continually influence medical action. In archaic times, symptoms of disease were explained as localized demons against which were used exorcisms, magic spells or offers of appeasement. Demons were also banned in a more active surgical manner by *ferrum caudens*. Even now, medical science must fight against the old demons and ghosts, but in a more hidden way. The old thought association—symptom—antisymptomatic medicament—still exists. The layman especially asks the doctor to follow this procedure. The primitive belief in miracles assumes that no disease exists without a counter medicament. Such thinking of course leads to a polypragmatic therapy that can be compared with the application of the miraculous arcanum in the Middle Ages, so-called Teriac—a mixture of innumerable magic substances—which served to cure all kinds of symptoms.

Nevertheless, symptomatic therapy can be important if therapeutic science fails and if one is able to relieve and to alleviate suffering. In this connection we should mention the narcotic drugs. When they are used well, they belong to the best means of symptomatic treatment mankind possesses. What physician would want to work without them! But subconsciously the drug fortifies the suggestion

that an outside medicament can expel the inside demon. The same narcotics can play havoc with the human being, can enslave him and bring him closer to the uncontrolled fantasies of primitive people.

Even surgery is scientifically described as symptomatic therapy. Surgery also expels affected parts of the body which have become dangerous or without value because of pathologic processes. Surgery interferes with biologic processes which cannot be influenced by physiologic therapeutic means because of lack of sufficient medical knowledge. That is why the ideal of good surgery is to make itself superfluous.

Transference and Countertransference

There is a continual and mutual relationship between doctor and patient. The patient wants his physician to be a god, a magician, a miracle worker. When he trusts his doctor, he subconsciously feels that every medicament has magic curative powers. The doctor needs such a transference from his patient. It is more than 50 per cent the secret of his cure. One doctor is better able than another to provide such transference. In everyday practice we call it "bedside manner" or "therapeutic instinct." The psychologist assumes that in this doctor-patient relationship all sorts of earlier relationships in the patient's life are repeated. The doctor must be aware that in every sick room, during every disease, the old drama of the helpless child in a hostile world is repeated and the physician represents the almighty parent who gives new power and confidence for the future.

But every relationship is reciprocal and the doctor also transfers to the patient his miseries, his sorrows and his hopes. The patient influences him. That is why he may fail because, due to unconscious reasons, he is not aware that he may be neglecting his patient, or that he is falling in love with him or her and that he feels confused because of this. As a result, the prescribing hand may write the wrong formula!

There is a vast range of subjective feelings between doctor and patient. Sometimes the patient wants the doctor's suggestions very badly because of their "magic" action, as is true in hypnotherapy. Sometimes the doctor communicates to the patient things he does not believe himself, but which he thinks are good for the patient. Although this happened more when medical psychology was not as well developed as it is today, this simple form of bedside psychology is still in use. Think, for example, of that innocent bottle of medicine, the placebo. According to scientific rules, it does not act pharmaceutically, but the patient swallows a spoonful of consoling suggestion every two hours. This kind of old-fashioned suggestion is often used in therapy. The general practitioner evades the real psychologic situation that would bring him and the patient nearer to the basis of the complaints. Instead, the doctor treats these with a pharmacologic lie. But I must say those suggestive medicaments help the simple-minded, and what philosopher does not become simple-minded when he is ill!

In former times, physicians prescribed rather drastic medicaments because of their suggestive action, such as asafetida. In modern times, it is done more elegantly with all kinds of nerve tonics, hormones and vitamins—the manifold, magic medicaments for nervous complaints. The choice is usually dependent upon the therapeutic mode and the influence of the local drugstore.

It isn't always the patient who asks for such an easy, acceptable suggestion. Often the doctor has to calm parents or frightened relatives with such prescriptions or other forms of fascinating treatment. Modern therapy helps him with glamorous and glittering electronic machines to sustain the suggestion. A tremendous resistance exists against rational therapy; the public wants magic machines!

The "Indicatio Utque Fiat"

A well known practitioner told me, with a large degree of self criticism, that 90 per cent of his therapy occurred as follows: The patient asked for something; the doctor's medical skepticism delayed a decision, but his prescribing hand was already moving. The other 10 per cent of his patients urged him to think about their real medical problems. These pa-

tients did not ask for immediate therapy. Especially during consultation hours, large numbers of patients force the doctor to use this reflexive prescribing hand. In the beginning, he may resist such action, but later he begins to believe in his automatic writing. This is a scientific danger—the belief that no disease is allowed to exist without medical intrusion.

The *indicatio utque fiat* paralyzes true medical experience.

The "Indicatio Pro Domo"

Medical action loses its objectivity when motivated by personal longings and subjective tendencies. We have seen the examples already in the process of countertransference. I do not like to underline here all the faulty motivations found in myself and in my colleagues, for I am sure that we detect the same egotistic factors in other professions. But, in the medical profession, it is often easier to hide private emotional investments behind pseudoscientific, noble justifications. Sometimes a new, valueless therapy is started in hope of stimulating personal fame. At other times, we evade theoretical difficulties by oversimplification of therapy. How many neurotic conversions have lost their organs and not their disease on the operating table? Specialization has had a bad influence on our general medical view, because every specialist is influenced by his particular scientific and economic interests. We must be aware of the fact that, in our therapeutic directive, unconscious motivations may influence our thoughts. These may be not only hidden, aggressive or sadistic traits, but also unconscious needs to be a healer and a god—as impractical and deceiving as unconscious sadism.

The patient too may suggest very interesting, inopportune treatments—a miraculous therapy, for instance, in order to become famous in the family, or his masochistic needs seek mutilating operations or depriving diets. Here we arrive gradually at psychopathology.

Enough of therapeutic directives! There are moments when the doctor becomes conscious of the motivations that lead to his actions. Yet there is still no therapeutic discipline that guides us against all the confusing and seducing suggestions of everyday life in the realm of treatment.

If we realize how exact our diagnostic knowledge already is, and, at the same time, if we realize what a difference there is between scientific diagnostic knowledge and therapeutic art, then we know how grateful we should be that medical schools provide us with a minimum number of clear therapeutic directives.

Nevertheless, at every moment on our way to better science we must look back with a critical view, for without this we become "polypragmatists," who fall for every new suggestion. We must realize that in every practical case we must depart from our scholastic precepts and individualize each case. For, in practice, we must treat patients and not schemes. Objective scientific indication will remain, because it will always relate personal therapeutic art to impersonal science. Human contact with the patient and the impersonal appraisal of scientific knowledge must together form what one may call the real medical art!

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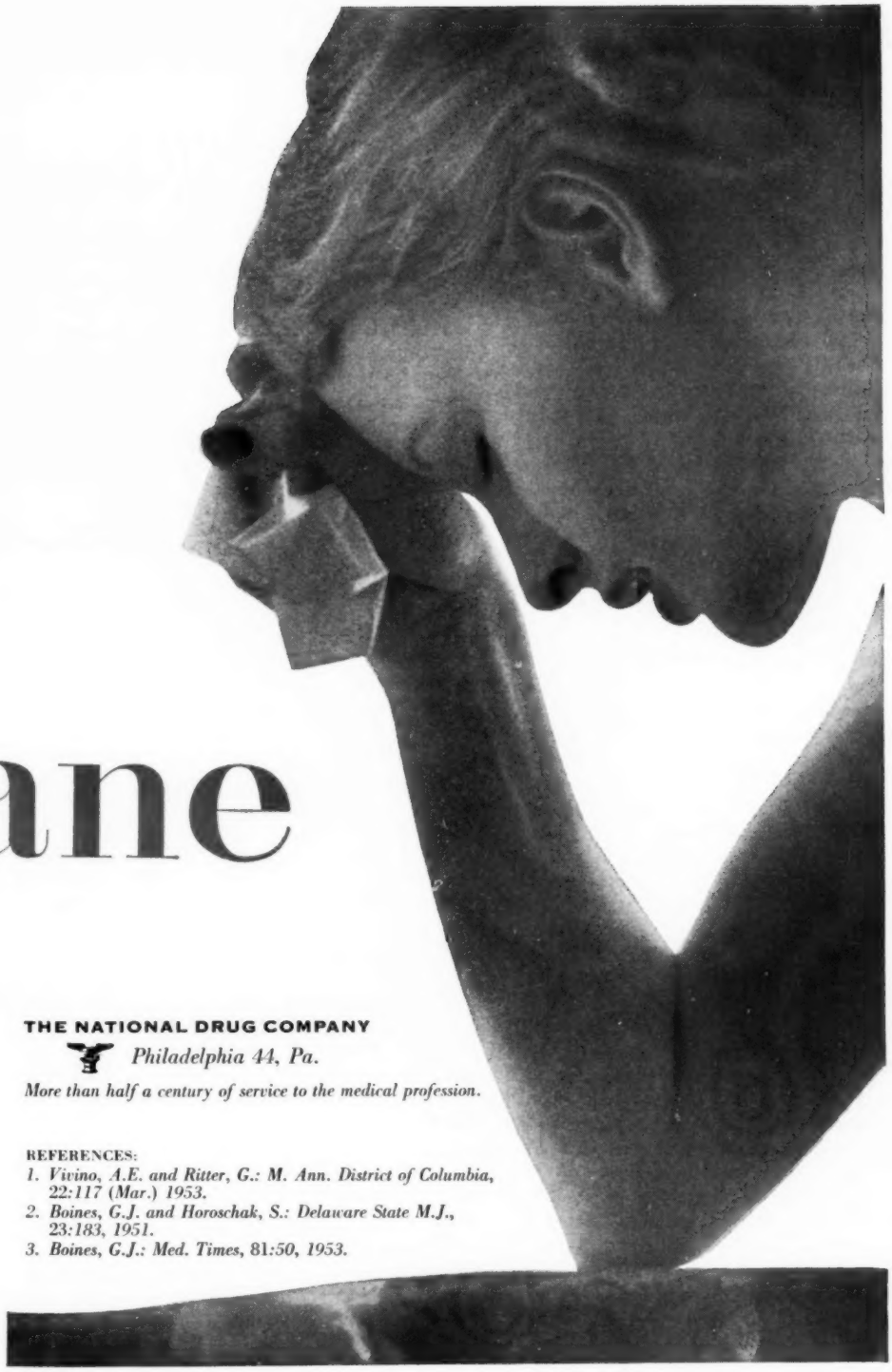

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THE MEDICAL Bookman

► SURGERY OF THE PANCREAS

By Richard B. Cattell, M.D. and Kenneth W. Warren, M.D., The Lahey Clinic, New England Baptist Hospital and New England Deaconess Hospital, Boston, Massachusetts. 374 pages with 100 figures. 1953, W. B. Saunders Company, Philadelphia & London. $10.00.

"Surgery of the Pancreas" is an excellent practical book which deals with surgical lesions of the pancreas. In this presentation, in which illustrations and tables are generously employed, the authors not only offer a review of their own wide personal experience in dealing with lesions of this type but also present the accumulated experience of the Lahey Clinic. Written primarily for the practicing clinical surgeon rather than the undergraduate, the book gives a clear and concise review of past experiences as well as current opinions. The authors are careful to indicate that, since surgery of the pancreas is a relatively new field, opinions of today may not coincide with those of tomorrow.

Anatomy and physiology of the pancreas are reviewed from a practical clinical and surgical point of view, but most of the book is devoted to diagnosis, clinical management, surgical indications and procedures in cases of various pancreatic lesions. These lesions include congenital malformations such as aberrant and annular pancreas, acute and chronic relapsing pancreatitis and its various complications, hyperinsulinism and carcinoma of the head of the pancreas and periampullary region. One chapter reviews experience to date with total pancreatectomy. Controversial subjects are discussed frankly and various views given, including those of the authors. Especially fine discussions on such interesting subjects as chronic relapsing pancreatitis, injuries of the pancreas, including the pancreatic ducts, and carcinoma of the pancreas and hyperinsulinism are presented.

Surgical technic, which for the most part is presented in general terms, is detailed for performance of the Whipple operation and comparable difficult procedures. Carefully prepared case reports are used liberally to emphasize points of particular clinical or surgical significance. Bibliographic references include significant previous contributions to the field. The large experience of the authors makes this an authoritative presentation and valuable reference.

J. T. P.

► PEDIATRICS

By L. Emmett Holt, Jr., Professor of Pediatrics, New York University College of Medicine, and Rustin McIntosh, Carpentier Professor of Pediatrics, Columbia University, New York City. Ed. 12. 1,485 pages with 272 figures. 1953, Appleton-Century-Crofts, Inc., New York. $15.00.

The twelfth edition of "Pediatrics" by Holt and McIntosh brings up-to-date one of the standard pediatric texts, first appearing in 1896. There has been extensive revision of the subject matter with due recognition being given to the more recent advances in diagnosis and therapeutics. There are 72 collaborators whose special interests have been utilized to fill out the substance of the text.

The book is divided conventionally into chapters on the newborn and premature infant, nutritional disturbances, deficiency diseases, and diseases according to the various organ systems of the body. The space devoted to infectious diseases has dwindled as their occurrence in practice has diminished, to be replaced by information on illnesses of current interest such as collagen diseases, viral hepatitis, coxsackievirus diseases, viral infections of the respiratory tract and retrolental fibroplasia. Due attention is given newer knowledge of hormonal therapy with corticotropin and cortisone, in-

(Continued on page A-82)

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cluding specific dosage schedules, and the chemotherapy of tuberculosis has received its proper share of attention. Favorable mention should also be made of the writing on the endocrine glands, on allergy and on psychopathologic problems in light of the current interest they assume in pediatric practice.

Among the miscellaneous diseases are grouped reticuloendotheliosis, disorders of lipoid metabolism, anomalies of carbohydrate, protein and electrolyte metabolism, the porphyrias, amyloidosis and acrodynia. A very useful and timely chapter on accidents and poisonings concludes the book. This is valuable in view of the frequency with which these are found as a cause of disease or death in young children today.

The appendix contains many tables of data on growth and development as well as data on standards of normal osseous development and a list of normal values for various blood chemical procedures and other laboratory tests of interest to the pediatrician.

The book is printed in very legible type and the text is profusely illustrated with many photographs, colored pictures, graphs and tables to amplify the subject material. A few of the photographs will be familiar to readers of this text in its earlier editions; most, however, are new, and they are appropriate to the subject matter. One could wish that they might have been reproduced more clearly to show what was intended. One could also wish that the references that follow each subject might have been more up-to-date as some go back to work which was done years ago and which in many cases has been superseded by newer and better information on the subject in question.

The book brings current concepts of diagnosis and treatment to the pediatrician faced with the problems of today's practice. It will continue to be a valuable textbook and reference for medical students and general practitioners interested in modern methods of handling their patients.

S. D. M.

► CONTACT DERMATITIS

By George Waldbott, M.D., Senior Physician, Harper Hospital, Detroit, Michigan. 218 pages with 332 illustrations. 1953, Charles C Thomas, Springfield, Illinois. $8.75.

Here is a textbook of dermatology written with the inquisitive, searching approach of the allergist. The text discusses the mechanism of contact sensitivity and compares it with atopic sensitivity. The author compares pathology with the clinical findings and the differential diagnosis that is to be made in the consideration of the dermatologic condition. It is readily apparent that differential diagnosis is handled in a careful way in order to separate contact dermatitis from the numerous other dermatitides that can affect particular areas. This is especially true with reference to the hands, a topic which is handled in very detailed fashion. The reason for concentration on the hands is obvious and points up the importance of this type of evaluation in patients from all walks of life, particularly those in industry.

Of exciting interest and importance is the matter of pattern in the dermatitis as outlined in this book. With numerous illustrations, the author indicates by ink markings the various sites of pressure and the patterns created by tools and agents which produce contact dermatitis, particularly on the palmar surfaces of the hands. The patterns of the various types are considered with regard to numerous instruments in occupation and in daily life and to the unusual sensitizers one might encounter. This is all handled so as to show what careful history and examination can reveal on the cause of a dermatitis.

In addition to the hands, there are of course other sites that may be involved, and these are given due consideration. The mode of determination of causes is outlined from the standpoint again of history taking and patch testing, as well as a careful diary on the part of the patient.

Dr. Waldbott handles the matter of dermatitis venenata, dermatitis from pollens, cosmetics, footwear and the many other hazards that one may encounter in daily living.

In pruritus involving the perianal region or the genitals, the author considers only the contact phases and omits the important psychosomatic aspects. This is no doubt deliberate in an effort to confine the text only to contact dermatitis.

Therapy is thoroughly considered from the standpoint of elimination of causative agents as well as that of desensitization. In addition, general measures of local care and handling of the entire individual are discussed.

I. F.

(Continued on page A-84)

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► ADVANCES IN PEDIATRICS; Volume 6

Edited by S. Z. Levine, M.D., Cornell University Medical College, New York. 323 pages, illustrated. 1953, The Year Book Publishers, Inc., Chicago. $7.50.

The sixth volume of "Advances in Pediatrics" is a collection of seven monographs on subjects of current interest to pediatricians and those dealing with the illnesses of childhood. The authors are recognized authorities in their fields and their presentations are lucid, comprehensive and well-documented by up-to-date, complete bibliographies. In gathering together present day information on the subjects listed, the authors have done a service to the reading physician and spared him many hours of effort in assembling pertinent material.

Five of the seven chapters deal with conditions met in the newborn period. The subjects and authors include: Lymphosarcoma in childhood by Dargeon; Preventive prenatal pediatrics by Ingalls; Intestinal obstruction in the neonatal period by Koop; Hemolytic disease of the newborn by Levine; Pulmonary pathology in the newborn by Potter; The Lipoidoses by van Creveld, and Megaloblastic anemia of infancy by Zuelzer and Rutzky. The book is well up to the standard of its predecessors and will be welcomed by readers of the former volumes of this series as well as others interested in pediatric problems.

S. D. M.

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► PAIN SYNDROMES AND THEIR TREATMENT

By James M. Tarsy, M.D., Assistant Clinical Professor of Medicine, Post-Graduate Medical School, New York University. 592 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $12.00.

When an expert on arthritis describes pain, one can expect a practical rather than a theoretical approach, and that is well set forth in this reference book. It might be helpful if someone would define "pain" for the benefit of the general practitioner. This book is primarily directed to the consideration of the pain syndromes arising from the cervical spine, thoracic inlet and shoulder girdle—very complicated because of the multitude of structures and their "neuromechanical" complexity. Since the technics of examination, diagnosis and treatment are equally important in general practice, neurology and arthritis, this should prove a very handy reference.

The anatomy of pain and its neuroanatomic concepts are clarified, leading to consideration of trigger mechanisms and the development of vicious circles. Sensory patterns and possible causes of pain syndromes are discussed. Specific consideration is then given the neck, shoulders and thorax, and clavicle, thoracic and shoulder lesions. Following reflex patterns, peripheral lesions are considered.

The indications, technic and values of local anesthesia and of therapeutic nerve block are presented at some length. The indications and contraindications are presented for various therapeutic agents.

Each chapter carries its own bibliography. Auxiliary bibliography of some 10 pages considers the over-all field to supplement the specific chapter. The index covers 24 pages and appears to be adequate. The book is well illustrated and should prove useful for all practitioners having to diagnose or treat pain syndromes.

J. C. M.

(Continued on page A-86)

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► SURGICAL PATHOLOGY

By Lauren V. Ackerman, M.D., Professor of Surgical Pathology and Pathology, Washington University, School of Medicine, St. Louis. 836 pages with 913 illustrations. 1953. The C. V. Mosby Company, St. Louis. $14.50.

A brand-new textbook by a well-known professor of pathology has just appeared. The author claims that it is only an introduction to the vast field of surgical pathology, the pathology of living. However, the medical student, the clinical pathologist, the surgeon and all physicians who are daily concerned with surgical pathology will find this book a most welcome addition to their library.

The introductory chapter contains much wholesome philosophy concerning the importance of thorough training in all branches of medicine as an adjunct to the qualifications for the successful practice of surgical pathology. The succeeding 24 chapters are arranged in a logical, anatomic manner and cover all the organ systems and parts of the body. The last chapter on the central nervous system was prepared by Dr. David E. Smith, assistant professor of pathology and surgical pathology at Washington University School of Medicine.

Eleven pages of admirably outlined table of contents, combined with 16 pages of carefully prepared index make this first edition very usable—features not always found in new books.

Approximately 90 per cent of the 913 illustrations are from negatives made at Washington University. These photographs of gross material, photomicrographs, and schematic diagrams form an excellent atlas for the instruction of the student, and a reference working tool for the surgical pathologist in his daily consultations. The other very important teaching feature is the complete list of references. While no key numbers have been used, any reference to an author's name in the text can easily be found in the bibliography at the end of each chapter or subdivision. The student should be urged to use this guide to his reading in the medical library for amplification of the information given only concisely in this excellent book.

A. H. S.

► DISEASES OF THE LIVER, GALLBLADDER AND BILE DUCTS

By S. S. Lichtman, M.D., Assistant Professor of Clinical Medicine, Cornell University Medical College, New York. Ed. 3. 1,315 pages with 220 illustrations and 3 color plates. 2 volumes. 1953, Lea & Febiger, Philadelphia. $22.00.

Since 1942 this work has been justifiably considered to be a very thorough and complete review of current knowledge of the anatomy, physiology and diseases of the liver and biliary system. In this, the third edition, the text has been extensively revised and new illustrations have been added. Revision has been particularly extensive in the chapters on anatomy, physiology and function of the liver, and viral hepatitis. The material added has required that the work now be published in two easily handled volumes instead of the single bulky one. The bibliography is excellent. The book should be in every medical library, and in that of any physician interested in diseases of the liver. Unfortunately, a number of minor typographic errors are scattered throughout the otherwise well-printed and well-arranged text.

C. B. L.

(Continued on page A-88)

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By Edward R. Schlesinger, M.D. 400 pages, 6 x 9. $7.50

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Slobody's

Survey of Clinical Pediatrics

By Lawrence B. Slobody, M.D. 471 pages, 6 x 9, illustrated. $7.50

Focusing on the highlights and relationships of pediatrics, this compact handbook covers every aspect of clinical pediatrics and provides all the material and references necessary to meet the demands of the average medical practice.

Hughes'

Pediatrics in General Practice

By James G. Hughes, M.D. 735 pages, 7¼ x 9⅞, illustrated. $14.00

A handy, concise reference on pediatrics specifically written to answer the need of busy general practitioners. Unique in its presentation of the pathologic physiology of disease states, the text stresses the more common conditions seen in general practice.

Chobot's

Pediatric Allergy

By Robert Chobot, M.D. 284 pages, 5½ x 8, illustrated. $6.00

Carefully discriminating the proven from the theoretical in a controversial field, this book will provide the general practitioner with authoritative information on pediatric allergy and guidance in his diagnosis and therapy.

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By Ross A. McFarland, Ph.D. 830 pages, 7¼ x 9⅞. $13.00

A wide range of facts and figures from the physiological, psychological, and engineering sciences have been integrated in this timely and comprehensive text for aviation medicine. Giving the aviation medical man an essential aid in his understanding of the aircraft environment and the limitations of human performance within it, the work presents very positive means whereby the broad principles of public health and safety may be applied to the physical and mental situation of men in the important field of air transportation.

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► MECHANISMS OF UROLOGIC DISEASE

By David M. Davis, M.D., Professor of Urology Emeritus, Jefferson Medical College, Philadelphia. 156 pages. 1953, W. B. Saunders Company, Philadelphia and London. $4.50.

According to the preface, ". . . it is time to systematize the body of urologic knowledge. This is particularly needed for beginners and for those physicians who are not urologic specialists. . . ." This is an extension of a syllabus for the use of medical students. Like Young's "Practice of Urology" it is arranged according to diseases rather than according to organs. Although the author states that "Illustrations have been judged inappropriate" your reviewer feels that well chosen ones would do much to enhance its value to those not already pretty familiar with urology.

This little book is concise and to the point, and contains a valuable bibliography. It is of value chiefly to medical students, interns and residents as a brief review and source of references. It will not be very useful to the practitioner who wants to refer to it to find out what to do about Mr. Smith's stones.

C. D. C.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

Copying and Duplicating Medical Subjects and Radiographs. By Lou Gibson, Technical Editor, Eastman Kodak Company, Rochester, New York. 75 pages, illustrated. 1953, Charles C Thomas, Springfield, Illinois. $5.00.

The Practical Management of Pain in Labour. By W. D. Wylie, M.A., Anaesthetist to St. Thomas's Hospital and The National Hospital for Nervous Diseases, London. 148 pages, illustrated. 1953, The Year Book Publishers, Inc., Chicago. $3.50.

The Major Metabolic Fuels. Number 5 of a series of symposiums sponsored by the Biology Department, Brookhaven National Laboratory, September 1952. 234 pages. 1953, Brookhaven National Laboratory, Upton, New York. Available from the Office of Technical Services, Department of Commerce, Washington 25, D.C. $1.35.

Psychosomatic Approach to Gynecology and Obstetrics. By Fritz Wengraf, M.D., Adjunct Neuropsychiatrist, Beth Israel Hospital, New York, New York. 346 pages. 1953, Charles C Thomas, Springfield, Illinois. $6.75.

Elementos de Medicina Infantil. By Dr. Carlos M. Monson Malice, University of San Carlos, Guatemala. 1951, University of Guatemala Press.

The Handbook of Sterilization and Disinfection. By John S. Beckett, B.Sc., and Phoebus Berman, M.D. 1953, Publishing Division of Aseptic-Thermo Indicator Company, North Hollywood, California. $2.50.

Peptic Ulcer; Pain Patterns, Diagnosis and Medical Treatment. By Lucian A. Smith, M.D., Assistant Professor of Medicine, Mayo Foundation and Head of Section, Division of Medicine, Mayo Clinic, and Andrew B. Rivers, M.D., Consultant, Division of Medicine, Mayo Clinic, Rochester, Minnesota. 576 pages, illustrated. 1953, Appleton-Century-Crofts, Inc., New York. $12.50.

Thoracic Surgery and Related Pathology. By Gustaf E. Lindskog, M.D., William H. Carmalt Professor of Surgery, and Averill A. Liebow, M.D., Professor of Pathology, Yale University School of Medicine, New Haven, Connecticut. 644 pages with 285 figures. 1953, Appleton-Century-Crofts, Inc., New York. $15.00.

Operative Surgery. By Guy W. Horsley, M.D., Associate Professor of Surgery, and Isaac A. Bigger, M.D., Professor of Surgery, Medical College of Virginia, Richmond. Ed. 6, 2 volumes. Volume I: Technic; Fluid Balance; Anesthesia; Blood Vessels; Plastic Surgery; Chest Surgery; Breast; Hernia. Volume II: Abdominal Incisions; Stomach; Bowel; Liver; Pancreas-Spleen; Orthopedics; Urology; Gynecology; Neurosurgery. 1,579 pages with 1,274 figures. 1953, The C. V. Mosby Company, St. Louis. $30.00.

Slipped Capital Femoral Epiphysis. By Armin Klein, M.D., Robert J. Joplin, M.D., John A. Reidy, M.D. and Joseph Hanelin, M.D., Massachusetts General Hospital, Boston. 130 pages with 77 figures. 1953, Charles C Thomas, Springfield, Illinois. $6.75.

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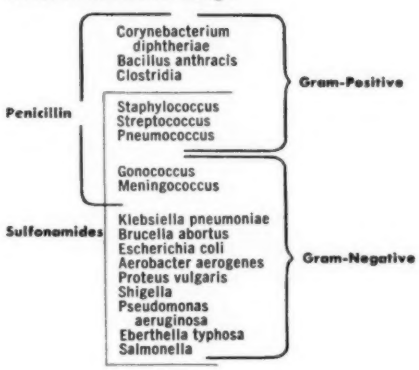

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